VERMONT
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Therapeutic Class Review
HMG-CoA Reductase Inhibitors – (Statins)
Combination Products

I. Overview

The combination hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (commonly referred to as "statins") include fixed-dose combinations of atorvastatin with amlodipine, lovastatin with extended-release niacin, and simvastatin with ezetimibe. All agents are formulated for oral administration. HMG-CoA reductase inhibitors work by inhibiting HMG-CoA reductase.[1] HMG-CoA reductase is the rate-limiting enzyme in the hepatic cholesterol synthesis, which catalyzes the conversion of HMG-CoA to mevalonate, a cholesterol precursor. Cholesterol synthesis reduction leads to the up-regulation of hepatic low-density lipoprotein cholesterol (LDL-C) receptors and subsequently an enhanced clearance of circulating LDL-C.

Niacin (nicotinic acid) is a water-soluble, B complex vitamin.[2] The exact mechanism by which niacin lowers cholesterol and triglycerides is not completely understood but is independent of the drug's role as a vitamin. Reductions in LDL-C through reduced hepatic synthesis of very low-density lipoprotein cholesterol (VLDL-C) are primarily responsible for the antilipemic effect of niacin.[2,3] Niacin may decrease production of VLDL-C by partially inhibiting mobilization of free fatty acids from adipose tissue, decreasing delivery of free fatty acids to the liver, decreasing triglyceride synthesis and altering the hepatic production of apolipoprotein B. Niacin increases high-density lipoprotein cholesterol (HDL-C) by reducing its catabolism.

Ezetimibe, a cholesterol absorption inhibitor, blocks dietary and biliary cholesterol absorption from the small intestine, leading to a decrease in hepatic cholesterol stores, an increase in hepatic cholesterol sequestering from the circulation, and ultimately lower systemic cholesterol levels.[4-7] Ezetimibe differs chemically and pharmacologically from other antilipemic agents, and because of its different mechanism of action it has been investigated for possible additive effects on lipid levels.[4,5] Clinical studies documented in the product information for ezetimibe showed that when used alone, it reduced LDL-C by up to 18% while increasing HDL-C by up to 3%.[5] Product information for the simvastatin-ezetimibe combination cites LDL-C reductions of up to 60% with an increase in HDL-C levels of up to 10%.[7]

Amlodipine is a dihydropyridine calcium-channel blocking agent that is indicated for the treatment of hypertension, for the treatment of chronic stable angina or vasospastic angina, and to reduce the risks of hospitalization or revascularization in patients with angiographically confirmed coronary artery disease (CAD).[8,9]

All combination statins are FDA-approved for the treatment of primary hyperlipidemia.[7,10,11] Atorvastatin-amlodipine and lovastatin-niacin extended-release combination products are also indicated for the prevention of cardiovascular events.[10,11] Simvastatin-ezetimibe lacks the indication for primary and/or secondary prevention of cardiovascular events.[7] In general, combination statins are appropriate when both components of the formulation are indicated.[4,10,12]

At present, no combination statins are available generically. Some of their components, namely lovastatin, simvastatin, and amlodipine, are available generically.[12] This review does not include information on Simcor®, a combination of simvastatin and extended-release niacin, which was reviewed separately by the DUR Board in June 2008.

Combination HMG-CoA reductase inhibitors that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths.

Table 1. Combination HMG-CoA Reductase Inhibitors Included in this Review

Generic Name*	Formulation(s)	Example Brand Name(s)
atorvastatin and amlodipine	tablet	Caduet®
lovastatin and niacin	extended-release tablet	Advicor®
simvastatin and ezetimibe	tablet	Vytorin®

*No generic products are available in this class.

All statins lower cholesterol levels. However, the degree to which individual agents lower cholesterol level varies. The lipid-lowering effects with combination statins are noted in Table 2. Other drug products contained within these combinations offer added benefits for the indications noted in Tables 4-6.

Table 2. Combination HMG-CoA Reductase Inhibitors Effects on Cholesterol Levels[7,10,11]

Drug	Daily Dosage	TC ↓ (%)	LDL-C ↓ (%)	TG ↓ (%)	HDL-C ↑ (%)
atorvastatin-amlodipine	10 mg–80 mg*	↓ 29-45	↓ 39-60	↓ 19-37	↑ 5-6
lovastatin-niacin	20 mg/1,000 mg to 40 mg/2,000 mg†	Not reported	↓ 30-42	↓ 32-44	↑ 20-30
simvastatin-ezetimibe	10 mg/10 mg to 80 mg/10 mg	↓ 31-43	↓ 45-60	↓ 23-31	↑ 6-8

HDL-C=high-density lipoprotein cholesterol, LDL-C =low-density lipoprotein cholesterol, TC=total cholesterol, TG=triglycerides
*The LDL-C lowering effect found in the atorvastatin-amlodipine package insert was attributed only to atorvastatin monotherapy; the figures for this combination are calculated from two studies of atorvastatin therapy in patients with primary hypercholesterolemia.
†Based on the package insert; the lower limit in these ranges is for patients titrated up to the 20 mg/1,000 mg dose over 12 weeks; the upper limit is for the same patients titrated up to the maximum dose of 40 mg/2,000 mg daily over 28 weeks.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate combination HMG-CoA reductase inhibitors (statins) are summarized in Table 3.

Table 3. Treatment Guidelines Using the Combination HMG-CoA Reductase Inhibitors

Clinical Guideline	Recommendation
National Heart, Lung, and Blood Institute (NHLBI)/American College of Cardiology (ACC)/American Heart Association (AHA): **Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines (2004)[13]**	• Therapeutic lifestyle changes (TLC) remain an essential modality in clinical management. • When low-density lipoprotein cholesterol (LDL-C)-lowering drug therapy is employed in high-risk or moderately high-risk persons, it is advised that intensity of therapy be sufficient to achieve at least a 30%-40% reduction in LDL-C levels. If drug therapy is a component of cholesterol management for a given patient, it is prudent to employ doses that will achieve at least a moderate-risk reduction. • Standard statin doses are defined as those that lower LDL-C levels by 30%-40%. The same effect may be achieved by combining lower doses of statins with other drugs or products (eg, bile acid sequestrants, ezetimibe, nicotinic acid, or plant stanols/sterols). • When LDL-C level is well above 130 mg/dL (eg, ≥160 mg/dL), the dose of statin may have to be increased or a second agent (eg, a bile acid sequestrant, ezetimibe, or nicotinic acid) may be required. Alternatively, maximizing dietary therapy (including use of plant stanols/sterols) combined with standard statin doses may be sufficient to attain goals. For the treatment of heterozygous familial hypercholesterolemia (FH) • Begin LDL-C-lowering drugs in young adulthood. • TLC indicated for all persons. • Statins: first line of therapy (start dietary therapy simultaneously).

Clinical Guideline	Recommendation
	• Bile acid sequestrants (if necessary in combination with statins). • If needed, consider triple-drug therapy (statins and bile acid sequestrants and nicotinic acid). For the treatment of homozygous FH • Statins may be moderately effective in some persons. • LDL-pheresis currently employed therapy (in some persons, statin therapy may slow down rebound hypercholesterolemia). For the treatment of familial defective apolipoprotein B-100 (FDB) • TLC indicated. • All LDL-C-lowering drugs are effective. • Combined drug therapy required less often than in heterozygous FH. For the treatment of polygenic hypercholesterolemia • TLC indicated for all persons. • All LDL-C-lowering drugs are effective. • If necessary to reach LDL-C goals, consider combined drug therapy.
National Institutes of Health (NIH), National Cholesterol Education Program (NCEP): **Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III [ATP III]) Final Report (2002)**[14]	General Recommendations • With regards to TLC, higher dietary intakes of omega-3 fatty acids in the form of fatty fish or vegetable oils are an option for reducing risk for coronary heart disease (CHD). This recommendation is optional because the strength of evidence is only moderate at present. NCEP ATP III supports the AHA's recommendation that fish be included as part of a CHD risk-reduction diet. Fish in general is low in saturated fat and may contain some cardioprotective omega-3 fatty acids. However, a dietary recommendation for a specific amount of omega-3 fatty acids is not made. • Initiate low-density lipoprotein (LDL)-lowering drug therapy with a statin, bile acid sequestrant or nicotinic acid. • Statins should be considered as first-line drugs when LDL-lowering drugs are indicated to achieve LDL-C treatment goals. • After 6 weeks if LDL-C goal is not achieved, intensify LDL-lowering therapy. Consider a higher dose of a statin or add a bile acid sequestrant or nicotinic acid. Statins • Statins should be considered as first-line drugs when LDL-lowering drugs are indicated to achieve LDL treatment goals.
American Heart Association (AHA)/American College of Cardiology (ACC) National Heart, Lung, and Blood Institute (NHLBI): **AHA/ACC Guidelines for Secondary Prevention for Patients With Coronary and Other Atherosclerotic Vascular Disease: 2006 Update (2006)**[15]	• For patients without atherosclerotic disease, including those with other risk factors, recommendations of the NCEP ATP III guidelines and their 2004 update should still be considered current. • Therapeutic options to reduce non–high-density lipoprotein cholesterol (HDL-C) include the following: more intense LDL-C lowering therapy, or niacin (after LDL-C lowering therapy) or fibrate therapy (after LDL-C lowering therapy).
Institute for Clinical Systems Improvement (ICSI): **Healthcare Guideline: Lipid Management in Adults (2007)**[16]	• For monotherapy, statins are the drugs of choice for lowering LDL. • If a patient is intolerant to a statin, other statins should be tried before ruling them all out. • If patients are unable to take statins, then bile acid sequestrants, ezetimibe, fibric acids and niacin can be used.

Clinical Guideline	Recommendation
	• Although combination therapy is not supported by outcome-based studies, some high-risk patients will require it. • Using low doses of two complementary agents can often reduce LDL to a greater extent than a higher dose of either agent, such as when a statin is combined with either ezetimibe or a bile acid sequestrant, with fewer side effects. • In very resistant cases, triple therapy may be needed.
American Heart Association (AHA): **Drug Therapy of High-Risk Lipid Abnormalities in Children and Adolescents: a Scientific Statement From the American Heart Association (2007)**[17]	• For children meeting criteria for lipid-lowering drug therapy, a statin is recommended as first-line treatment. The choice of statin is dependent upon preference but should be initiated at the lowest dose once daily, usually at bedtime. • For patients with high-risk lipid abnormalities, the presence of additional risk factors or high-risk conditions may reduce the recommended LDL level for initiation of drug therapy and the desired target LDL levels. Therapy may also be considered for initiation in patients <10 years of age. • Additional research regarding drug therapy of high-risk lipid abnormalities in children is needed to evaluate the long-term efficacy and safety and impact on the atherosclerotic disease process.
European Guidelines on Cardiovascular Disease Prevention in Clinical Practice: **Fourth Joint Task Force of the European Society of Cardiology (ESC) and Other Societies (2007)**[18]	• Statins are considered first-line drugs for lowering LDL-C. • Statins are considered first-line drugs for lowering LDL cholesterol. • When TG are between ~450-900 mg/dL, statins (or fibrates) may be considered as first-choice drugs. • Combination therapy may be used in patients needing additional therapy to reach goals and the selection of appropriate drugs should vary based upon lipid levels.

III. Indications

All HMG-CoA reductase inhibitors (statins) should be used as adjuncts to a diet restricted in saturated fat and cholesterol for the reduction of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) in patients with primary hypercholesterolemia.[1,19-22] Combination statins should not be used as initial therapy but have a role in the consolidation of therapy in patients already stabilized on the separate entities. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

As monotherapy, ezetimibe is indicated as adjunctive therapy to diet for the reduction of elevated TC, LDL-C, and apolipoprotein (apo) B in patients with primary (heterozygous familial and nonfamilial) hypercholesterolemia.[5] Ezetimibe monotherapy is also indicated in patients with homozygous familial sitosterolemia.[5] FDA-approved indications for the simvastatin-ezetimibe combination product (Vytorin®) are noted in Table 4. Note that the effects of simvastatin-ezetimibe on cardiovascular morbidity/mortality end points have not yet been established.[7]

The atorvastatin-amlodipine combination product (Caduet®) is indicated in patients for whom treatment with both atorvastatin and amlodipine is appropriate.[10] Food and Drug Administration (FDA)-approved indications for atorvastatin are noted in Table 4, and those for amlodipine in Table 5.[10]

The lovastatin-niacin combination product (Advicor®) is indicated in patients for whom treatment with both lovastatin and extended-release niacin is appropriate.[11] FDA-approved indications for lovastatin are noted in Table 4, and those for extended-release niacin (Niaspan®) in Table 6.

Table 4. FDA-Approved Indications for Atorvastatin, Lovastatin, and Simvastatin-Ezetimibe[5,7,10,11,19-21]

Indication	Atorvastatin	Lovastatin	Simvastatin-Ezetimibe
Prevention of Cardiovascular Disease			
Primary prevention of cardiovascular events (patients without clinically evident coronary heart disease [CHD]); to reduce the risk of:	✔ *†	✔	
Angina	✔ *	✔ ‡ (Unstable)	
Myocardial infarction	✔ *†	✔ ‡	
Revascularization procedures	✔ *	✔ ‡ (Coronary)	
Stroke	✔ *†		
Secondary prevention of cardiovascular events (patients with clinically evident CHD) to reduce the risk of:	✔		
Angina	✔		
Hospitalization for congestive heart failure (CHF)	✔		
Myocardial infarction (nonfatal)	✔		
Revascularization procedures	✔		
Stroke (fatal and nonfatal)	✔		
Coronary atherosclerosis, slowing its progression in patients with CHD, as part of a treatment strategy to lower total and low-density lipoprotein cholesterol (LDL-C) to target levels		✔	
Treatment of Dyslipidemias			
Primary hypercholesterolemia (heterozygous familial and nonfamilial; Fredrickson Type IIa) and mixed dyslipidemia (Fredrickson Type IIb)	✔ §	✔ §	✔ §
To reduce:			
TC	✔	✔	✔
LDL-C	✔	✔	✔
Apo B	✔		✔
Triglyceride (TG)	✔		✔
Non– high-density lipoprotein cholesterol (HDL-C)			✔
To increase:			
HDL-C	✔		✔
Homozygous familial hyperlipidemia, as an adjunct to other lipid-lowering treatments (eg, low-density lipoprotein [LDL] apheresis) or if such treatments are unavailable	✔		✔
To reduce:			
TC	✔		✔
LDL-C	✔		✔
Primary dysbetalipoproteinemia (Fredrickson Type III)	✔	‖	
Hypertriglyceridemia, elevated serum TG levels (Fredrickson Type IV)	✔	‖	
Elevated chylomicrons (Fredrickson Types I and V)	‖	‖	
Heterozygous familial hypercholesterolemia (HeFH) in pediatric patients, 10-17 years old, boys and postmenarchal girls¶	✔ §	#	

*In adult patients with multiple risk factors for coronary heart disease such as age, smoking, hypertension, low HDL-C, or a family history of early coronary heart disease

†In patients with type 2 diabetes, and without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as retinopathy, albuminuria, smoking, or hypertension

‡In individuals with average to moderately elevated TC and LDL-C, and below average HDL-C

§As an adjunct to diet, or after inadequate response to diet and other nonpharmacological measures

‖ Has not been studied for this condition.

¶To reduce TC, LDL-C and apolipoprotein B levels if after an adequate trial of diet therapy the following findings are present:

1. LDL-C remains >189 mg/dL or
2. LDL-C remains >160 mg/dL and either (a) there is a positive family history of premature cardiovascular disease or (b) 2 or more other CVD risk factors are present

#Single-entity lovastatin is indicated as an adjunct to diet, or after inadequate response to diet and other nonpharmacological measures, for heterozygous familial hypercholesterolemia in boys and postmenarchal girls 10-17 years old; however, the combination lovastatin-niacin product (Advicor®) is not indicated in this population.

Table 5. FDA-Approved Indications for Amlodipine[9,10]

Indication	Amlodipine
For the treatment of hypertension, alone or in combination with other antihypertensive agents	✔
For the treatment of chronic stable angina, alone or in combination with other antianginal or other antihypertensive agents	✔
For the treatment of confirmed or suspected vasospastic angina (Prinzmetal's or variant angina), alone or in combination with other antianginal agents	✔
In patients with recently documented coronary artery disease by angiography, without heart failure or an ejection fraction <40%, to reduce the risk of hospitalization due to angina and to reduce the risk of a coronary revascularization procedure	✔

Table 6. FDA-Approved Indications for Extended-Release Niacin (Niaspan®)[23]

Indication	Niacin, Extended-Release (Niaspan®)
Adjunct to diet for reduction of elevated TC, LDL-C, apo B and TG levels, and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson Types IIa and IIb) when the response to an appropriate diet has been inadequate	✔
In combination with lovastatin, treatment of primary hypercholesterolemia and mixed dyslipidemia	✔
To reduce the risk of recurrent nonfatal myocardial infarction in patients with a history of myocardial infarction and hypercholesterolemia	✔
Adjunctive therapy for treatment of adult patients with very high serum triglyceride levels (Fredrickson Types IV and V hyperlipidemia) who present a risk of pancreatitis and who do not respond adequately to a determined dietary effort to control them	✔

*Unlike extended-release niacin (Niaspan®), the lovastatin-niacin combination product (Advicor®) is not indicated in combination with bile acid binding resins.

IV. Pharmacokinetics

The pharmacokinetic parameters for the combination HMG-CoA reductase inhibitors (statins) are summarized in Table 7. Minor differences exist between the statins in regards to pharmacokinetic parameters. Half-life is one parameter that separates some statins from others. The pharmacokinetic parameters of the combination products are not significantly different from the pharmacokinetic parameters of the individual components.

Table 7. Pharmacokinetic Parameters of the Combination HMG-CoA Reductase Inhibitors[5-11,19-25]

Drug(s)	Absolute Bioavailability (%)	Protein Binding (%)	Lipid Solubility	Metabolism	Active Metabolites	Half-Life (hours)
Atorvastatin-amlodipine	14; 64-90	≥98; 93	Hydrophilic; not reported	Hepatic, CYP3A4	Yes, 2-hydroxy- and 4-hydroxy-atorvastatin acid; None	14-30; 30-50
Lovastatin-niacin	<5; 60-76	>95; 20	Lipophilic; not reported	Hepatic, CYP3A4; Hepatic	Yes, beta-hydroxyacid and 6-hydroxy derivatives; Yes, nicotinamide adenine dinucleotide	1.1-4.5; 0.3-0.8
Simvastatin-ezetimibe	5; Not reported	95; >90	Lipophilic; not reported	Hepatic, CYP3A4; Hepatic, glucuronide conjugation	Yes, beta-hydroxyacid of simvastatin; Yes, ezetimibe glucuronide	Not reported; 22

V. Drug Interactions

Significant drug interactions with the combination HMG-CoA reductase inhibitors (statins) are listed in Table 8. The drug interactions with the combination products are not significantly different from the drug interactions with the individual components.

Table 8. Significant Drug-Drug Interactions with the Combination HMG-CoA Reductase Inhibitors[6]

Drug(s)	Significance Level	Interaction	Mechanism
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, simvastatin)	1	Amiodarone	Amiodarone may decrease the elimination of certain HMG-CoA reductase inhibitors by inhibiting their metabolism via CYP3A4 resulting in increased concentration and consequently increased pharmacologic and toxic effects (ie, myositis, rhabdomyolysis) of HMG-CoA reductase inhibitors. Decrease HMG-CoA reductase inhibitor dose accordingly; monitor for toxicity. Fluvastatin, pravastatin, and rosuvastatin are not metabolized by CYP3A4 and may be safer alternatives.
HMG-CoA reductase inhibitors (all)	1	Azole antifungals (fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole)	Azole antifungal agents may decrease the elimination of HMG-CoA reductase inhibitors by inhibiting their first-pass hepatic metabolism via CYP3A4/CYP2C9 isoenzymes resulting in increased concentration and consequently increased pharmacologic and toxic (ie, rhabdomyolysis) effects of HMG-CoA reductase inhibitors. Itraconazole is contraindicated with HMG-CoA reductase inhibitors metabolized by CYP3A4. If other azole antifungals are to be used, HMG-CoA reductase inhibitor dose should be decreased accordingly. Patients should be monitored for toxicity. Pravastatin may be a safer alternative since its levels are affected least by azole coadministration.
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin)	1	Cyclosporine	Cyclosporine may decrease the elimination of certain HMG-CoA reductase inhibitors by inhibiting their metabolism and resulting in increased concentration and consequently increased pharmacologic and toxic (ie, rhabdomyolysis) effects of HMG-CoA reductase inhibitors. Decrease HMG-CoA reductase inhibitor dose accordingly; monitor for toxicity.
HMG-CoA reductase inhibitors (all)	1	Fibric acid derivatives (fenofibrate, gemfibrozil)	Coadministration of fibric acid derivatives with HMG-CoA reductase inhibitors may result in myopathy or rhabdomyolysis via an unknown mechanism. Decrease HMG-CoA reductase inhibitor dose accordingly; obtain creatine kinase levels and monitor for toxicity.
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, simvastatin)	1	Macrolides and ketolides (clarithromycin, erythromycin and telithromycin)	Macrolides may decrease the elimination of certain HMG-CoA reductase inhibitors by inhibiting their metabolism via CYP3A4 resulting in increased concentration and consequently increased pharmacologic and toxic (ie, myopathy or rhabdomyolysis) effects of HMG-CoA reductase inhibitors. Decrease HMG-CoA reductase inhibitor dose accordingly; monitor for toxicity. Fluvastatin and pravastatin may be safer alternatives.
HMG-CoA reductase inhibitors (atorvastatin, lovastatin,	1	Nefazodone	Nefazodone may decrease the elimination of certain HMG-CoA reductase inhibitors by inhibiting their metabolism via CYP3A4 resulting in increased concentrations and increased pharmacologic and toxic (ie, rhabdomyolysis or myositis) effects of HMG-CoA reductase inhibitors. Decrease HMG-CoA reductase inhibitor dose

Drug(s)	Significance Level	Interaction	Mechanism
simvastatin)			accordingly; monitor for toxicity. Fluvastatin and pravastatin may be safer alternatives.
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, pravastatin, simvastatin)	1	Non-nucleoside reverse transcriptase inhibitors (NNRTIs) (delavirdine, efavirenz, nevirapine)	Delavirdine and nevirapine may inhibit the metabolism of HMG-CoA reductase inhibitors, via CYP3A4, resulting in increased concentration and consequently increased pharmacologic and toxic (ie, rhabdomyolysis or myopathy) effects of HMG-CoA reductase inhibitors. In contrast, efavirenz may induce CYP3A4 metabolism, resulting in decreased concentration and consequently decreased pharmacologic effects of HMG-CoA reductase inhibitors. With concurrent administration, adjust HMG-CoA reductase inhibitor dose accordingly; monitor plasma low-density lipoprotein cholesterol (LDL-C) level, and adverse effects.
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, simvastatin)	1	Grapefruit	Grapefruit may decrease the elimination of certain HMG-CoA reductase inhibitors by inhibiting their first-pass metabolism via CYP3A4, resulting in increased concentration and consequently increased pharmacologic and toxic (ie, rhabdomyolysis) effects of these HMG-CoA reductase inhibitors. Avoid concomitant administration of atorvastatin, lovastatin, and simvastatin with grapefruit products.
Lovastatin	1	Protease inhibitors (amprenavir, atazanavir, darunavir, indinavir, lopinavir/ritonavir, nelfinavir, ritonavir, saquinavir)	Protease inhibitors may decrease the elimination of lovastatin by inhibiting its metabolism via CYP3A4 resulting in increased concentration and consequently increased pharmacologic and toxic (ie, rhabdomyolysis) effects of lovastatin. Decrease lovastatin dose accordingly; monitor for toxicity. Lovastatin is contraindicated in patients receiving concomitant nelfinavir. In addition, lovastatin should not be coadministered with ritonavir, atazanavir, or darunavir.
Simvastatin	1	Protease inhibitors (amprenavir, atazanavir, darunavir, indinavir, lopinavir/ritonavir, nelfinavir, ritonavir, saquinavir)	Protease inhibitors may decrease the elimination of simvastatin by inhibiting its metabolism via CYP3A4 resulting in increased concentration and consequently increased pharmacologic and toxic (ie, rhabdomyolysis) effects of simvastatin. Simvastatin is contraindicated in patients receiving nelfinavir. In addition, coadministration of simvastatin with ritonavir or darunavir should be avoided.
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, simvastatin)	2	Carbamazepine	Carbamazepine may increase the clearance of certain HMG-CoA reductase inhibitors by inducing their metabolism via CYP3A4 resulting in decreased concentration and consequently decreased pharmacologic effects of HMG-CoA reductase inhibitors. Monitor patients for a decrease in clinical effect. Pravastatin and rosuvastatin may be safer alternatives.
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, simvastatin)	2	Diltiazem	Diltiazem may decrease the elimination of certain HMG-CoA reductase inhibitors by inhibiting their first-pass metabolism via CYP3A4 resulting in increased concentration and consequently increased pharmacologic and toxic (ie, rhabdomyolysis, myositis) effects of HMG-CoA reductase inhibitors. Pravastatin may be a safer alternative.
HMG-CoA reductase inhibitors (atorvastatin, fluvastatin,	2	Rifamycins (rifabutin, rifampin, rifapentine)	Rifamycins may increase the clearance of certain HMG-CoA reductase inhibitors by inducing their first-pass metabolism via CYP3A4 resulting in decreased concentration and consequently decreased pharmacologic effects of HMG-CoA reductase inhibitors. The dose of the HMG-CoA reductase inhibitor may need to be

Drug(s)	Significance Level	Interaction	Mechanism
lovastatin, pravastatin, simvastatin)			increased. Pravastatin levels may be increased in some patients.
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, simvastatin)	2	Verapamil	Verapamil may decrease the elimination of certain HMG-CoA reductase inhibitors by inhibiting their first-pass metabolism via CYP3A4 resulting in increased concentration and consequently increased pharmacologic and toxic (ie, rhabdomyolysis, myositis) effects of HMG-CoA reductase inhibitors. Decrease HMG-CoA reductase inhibitor dose accordingly; monitor for toxicity. Fluvastatin and pravastatin may be safer alternatives.
HMG-CoA reductase inhibitors (fluvastatin, lovastatin, rosuvastatin, simvastatin)	2	Warfarin	HMG-CoA reductase inhibitors may decrease the elimination of warfarin by inhibiting its hepatic metabolism resulting in increased anticoagulant effect of warfarin. Monitor patients' anticoagulant parameters when starting or discontinuing concurrent therapy with warfarin and HMG-CoA reductase inhibitors. Atorvastatin and pravastatin may be safer alternatives.
Atorvastatin	2	Protease inhibitors (amprenavir, indinavir, lopinavir/ritonavir, nelfinavir, ritonavir, saquinavir)	Protease inhibitors may decrease the elimination of atorvastatin by inhibiting its first-pass metabolism via CYP3A4 resulting in increased concentration and consequently increased pharmacologic and toxic (ie, rhabdomyolysis) effects of atorvastatin. Monitor patients receiving atorvastatin for toxicity, especially with ritonavir/saquinavir combination. Decrease atorvastatin dose accordingly; monitor for toxicity.
Ezetimibe	2	Cyclosporine	Coadministration of cyclosporine with ezetimibe may result in increased plasma concentration of both drugs via an unknown mechanism. Decrease ezetimibe dose accordingly; monitor for toxicity.

Significance Level 1=major severity
Significance Level 2=moderate severity

VI. Adverse Drug Events

All HMG-CoA reductase inhibitors (statins) may cause an elevation in liver enzymes and creatinine kinase, sometimes accompanied by myopathy and rarely rhabdomyolysis and renal failure.[1,6] Niacin therapy is also associated with serum transaminase elevations, as well as hyperglycemia and elevation in uric acid levels.[2] As with the single entity statins, liver function tests should be performed routinely with combination statin therapy.

The most common adverse reactions reported with the combination statins are noted in Table 9. The adverse drug event profile of the combination products is not significantly different from the adverse reaction profile of the individual components.

Table 9. Adverse Drug Events (%) Reported with the Combination HMG-CoA Reductase Inhibitors [5-11,19-25]

Adverse Event	Atorvastatin	Amlodipine	Lovastatin	Niacin ER	Simvastatin	Ezetimibe
Cardiovascular						
Angina pectoris	<2	-	-	-	-	-
Arrhythmia	<2	<1	-	✔	-	-
Bradycardia	-	<1	-	-	-	-
Cardiac failure	-	≤0.1	-	-	-	-
Chest pain	≥2	<1	0.5-1	-	-	-
Hypertension	<2	-	-	-	-	-

Adverse Event	Atorvastatin	Amlodipine	Lovastatin	Niacin ER	Simvastatin	Ezetimibe
Hypotension	-	<1	-	✔	-	-
Migraine	<2	≤0.1	-	✔	-	-
Phlebitis	<2	-	-	-	-	-
Palpitation	<2	≤4.5	-	✔	-	-
Peripheral ischemia	-	<1	-	-	-	-
Postural hypotension	<2	<1	-	✔	-	-
Vasodilatation	<2	-	-	-	-	-
Syncope	<2	<1	-	✔	-	-
Tachycardia	-	<1	-	✔	-	-
Central Nervous System/Neurological						
Abnormal dreams	<2	<1	-	-	-	-
Agitation	-	≤0.1	-	-	-	-
Amnesia	<2	≤0.1	-	-	-	-
Anxiety	-	<1	✔	-	✔	-
Apathy	-	≤0.1	-	-	-	-
Chills	-	-	✔	-	-	-
Cranial nerve dysfunction	-	-	✔	-	✔	-
Depression	<2	<1	✔	-	✔	-
Dizziness	≥2	≤3.4	0.5-2.0	-	✔	✔
Emotional lability	<2	-	-	-	-	-
Facial paralysis	<2	-	-	-	-	-
Fever	<2	-	✔	-	✔	-
Flushing	-	≤4.5	✔	≥5	✔	-
Headache	2.5-16.7	7.8	2.1-8.0	≥5	3.5	6-7
Hyperkinesia	<2	-	-	-	-	-
Hypertonia	<2	-	-	-	-	-
Hypesthesia	<2	<1	-	-	-	-
Incoordination	<2	-	-	-	-	-
Insomnia	≥2	<1	0.5-1	-	✔	-
Libido decreased	<2	-	✔	-	✔	-
Memory loss	-	-	✔	-	✔	-
Neck rigidity	<2	-	-	-	-	-
Paresthesia	<2	<1	0.5-1	-	✔	-
Peripheral nerve palsy	-	-	✔	-	✔	-
Peripheral neuropathy	<2	<1	✔	-	✔	-
Psychiatric disturbances	-	<1	✔	-	✔	-
Somnolence	<2	≤1.6	-	-	-	-
Torticollitis	<2	-	-	-	-	-
Tremor	-	<1	✔	-	✔	-
Vertigo	-	<1	✔	-	-	-
Dermatological						
Acanthosis nigricans	-	-	-	✔	-	-
Acne	<2	-	-	-	-	-
Alopecia	<2	≤0.1	0.5-1	-	✔	-
Contact dermatitis	<2	-	-	-	-	-
Dermatitis	-	≤0.1	-	-	-	-
Dry skin	<2	≤0.1	✔	-	-	-
Eczema	<2	-	-	-	0.8	-
Hyperpigmentation	-	-	-	✔	-	-
Pruritus	<2	<1	0.5-1	≥5	0.5	-
Rash	1.1-3.9	<1	0.8-1.3	≥5	0.6	✔

Adverse Event	Atorvastatin	Amlodipine	Lovastatin	Niacin ER	Simvastatin	Ezetimibe
Seborrhea	<2	-	-	-	-	-
Skin ulcer	<2	-	-	-	-	-
Sweating	<2	1-2	-	✔	-	-
Urticaria	<2	≤0.1	✔	-	-	✔
Endocrine and Metabolic						
Gout	<2	-	-	-	-	-
Hyperglycemia	<2	1-2	-	≥5	-	-
Hypoglycemia	<2	-	-	-	-	-
Peripheral edema	≥2	≤14.6	-	✔	-	-
Thirst	-	1-2	-	-	-	-
Weight gain	<2	-	-	-	-	-
Gastrointestinal						
Abdominal pain	0-3.8	1.6	2.0-2.5	≥5	0.9-3.2	✔
Acid regurgitation	-	-	0.5-1	-	-	-
Anorexia	<2	<1	✔	-	✔	-
Biliary pain	<2	-	-	-	-	-
Cheilitis	<2	-	-	-	-	-
Cholestatic jaundice	<2	✔	✔	-	✔	✔
Cirrhosis	-	-	✔	-	✔	-
Colitis	<2	-	-	-	-	-
Constipation	0-2.5	<1	2.0-3.5	-	2.3	-
Diarrhea	0-3.8	<1	2.2-2.6	≥5	0.5-1.9	✔
Dry mouth	<2	1-2	0.5-1	-	-	-
Duodenal ulcer	<2	-	-	-	-	-
Dyspepsia/heartburn	1.3-2.8	<1	1.0-1.6	≥5	0.6-1.1	-
Dysphagia	<2	<1	-	-	-	-
Enteritis	<2	-	-	-	-	-
Eructation	<2	-	-	-	-	-
Esophagitis	<2	-	-	-	-	-
Flatulence	1.1-2.8	<1	3.7-4.5	-	0.9-1.9	-
Fulminant hepatic necrosis	-	-	✔	-	✔	-
Gastritis	<2	≤0.1	-	-	-	-
Gastroenteritis	<2	-	-	-	-	-
Gingival hyperplasia	-	<1	-	-	-	-
Glossitis	<2	-	-	-	-	-
Gum hemorrhage	<2	-	-	-	-	-
Hepatitis	<2	-	✔	-	✔	✔
Hepatoma	-	-	✔	-	✔	-
Increased appetite	<2	≤0.1	-	-	-	-
Melena	<2	-	-	-	-	-
Mouth ulceration	<2	-	-	-	-	-
Nausea	≥2	2.9	1.9-2.5	≥5	0.4-1.3	✔
Pancreatitis	<2	<1	✔	-	✔	✔
Rectal hemorrhage	<2	-	-	-	-	-
Stomach ulcer	<2	-	-	-	-	-
Stomatitis	<2	-	-	-	-	-
Ulcerative stomatitis	<2	-	-	-	-	-
Vomiting	<2	<1	0.5-1	≥5	✔	-
Genitourinary						
Abnormal ejaculation	<2	-	-	-	-	-
Albuminuria	≥2	-	-	-	-	-

Adverse Event	Atorvastatin	Amlodipine	Lovastatin	Niacin ER	Simvastatin	Ezetimibe
Breast enlargement	<2	-	-	-	-	-
Cystitis	<2	-	-	-	-	-
Dysuria	<2	≤0.1	-	-	-	-
Epididymitis	<2	-	-	-	-	-
Erectile dysfunction	-	-	✔	-	✔	-
Fibrocystic breast	<2	-	-	-	-	-
Gynecomastia	-	✔	✔	-	✔	-
Hematuria	≥2	-	-	-	-	-
Impotence	<2	-	-	-	-	-
Kidney calculus	<2	-	-	-	-	-
Metrorrhagia	<2	-	-	-	-	-
Nephritis	<2	-	-	-	-	-
Nocturia	<2	1-2	-	-	-	-
Sexual dysfunction	-	<1	-	-	-	-
Urinary abnormality	-	1-2	-	-	-	-
Urinary frequency	<2	1-2	-	-	-	-
Urinary incontinence	<2	-	-	-	-	-
Urinary retention	<2	-	-	-	-	-
Urinary tract infection	≥2	-	3.0	-	-	-
Urinary urgency	<2	-	-	-	-	-
Uterine hemorrhage	<2	-	-	-	-	-
Vaginal hemorrhage	<2	-	-	-	-	-
Hematologic						
Anemia	<2	-	-	-	-	-
Ecchymosis	<2	-	-	-	-	-
Eosinophilia	-	-	✔	-	✔	-
Hemolytic anemia	-	-	✔	-	✔	-
Leukopenia	-	1-2	✔	-	✔	-
Lymphadenopathy	<2	-	-	-	-	-
Petechia	<2	-	-	-	-	-
Purpura	-	1-2	✔	-	✔	-
Thrombocytopenia	<2	1-2	✔	-	✔	-
Vasculitis	-	<1	✔	-	✔	-
Laboratory Test Abnormalities						
Creatine phosphokinase increased	<2	-	-	-	✔	✔
Bilirubin elevation	-	-	✔	-	✔	-
Hematuria	-	-	-	-	-	-
Liver enzyme abnormalities	-	✔	✔	-	✔	✔
Proteinuria	-	-	-	-	-	-
Thyroid level abnormality	-	-	✔	-	✔	-
Musculoskeletal						
Arthritis	≥2	<1	0.5-6	-	✔	-
Arthralgia	-	<1	-	✔	✔	✔
Back pain	0-3.8	<1	5.0	≥5	-	✔
Bursitis	<2	-	-	-	-	-
Hypertonia	-	≤0.1	-	-	-	-
Leg cramps	<2	-	-	-	-	-
Muscle cramps	-	<1	0.6-1.1	-	✔	-
Myalgia	-	<1	1.8-3.0	≥5	1.2	2.3-4
Myopathy	-	-	-	✔	✔	✔

Adverse Event	Atorvastatin	Amlodipine	Lovastatin	Niacin ER	Simvastatin	Ezetimibe
Myositis	<2	-	-	-	-	-
Myasthenia	<2	≤0.1	-	-	-	-
Polymyalgia rheumatica	-	-	✔	-	✔	-
Rhabdomyolysis	✔	-	✔	✔	✔	✔
Tendinous contracture	<2	-	-	-	-	-
Tendon rupture	✔	-	-	-	-	-
Tenesynovitis	<2	-	-	-	-	-
Respiratory						
Asthma	<2	-	-	-	-	-
Bronchitis	≥2	-	-	-	-	-
Cough	-	≤0.1	-	-	-	✔
Dyspnea	<2	<1	✔	-	✔	-
Epistaxis	<2	<1	-	-	-	-
Pharyngitis	0-2.5	-	-	-	-	✔
Pneumonia	<2	-	-	-	-	-
Rhinitis	≥2	≤0.1	-	✔	-	-
Sinusitis	0-6.4	-	6.0	-	-	✔
Upper respiratory infection	-	-	-	-	2.1	5
Other						
Abnormal vision	-	1-2	0.9-1.2	-	-	-
Accidental injury	0-4.2	-	4	-	-	-
Allergic reaction	0-2.8	<1	-	-	-	-
Amblyopia	<2	-	-	-	-	-
Anaphylaxis	✔	-	✔	-	✔	✔
Angioedema	-	<1	✔	-	✔	✔
Angioneurotic edema	✔	-	-	-	-	-
Asthenia	0-3.8	<1	1.2-2.0	≥5	1.6	-
Cataracts	-	-	✔	-	0.5	-
Conjunctivitis	-	1-2	-	-	-	-
Dry eyes	<2	-	-	-	-	-
Erythema multiforme	<2	<1	✔	-	✔	-
Eye hemorrhage	<2	-	-	-	-	-
Eye irritation	-	-	0.5-1	✔	-	-
Facial/general edema	<2	-	-	✔	-	-
Fatigue	✔	4.5	-	-	-	✔
Flu syndrome	0-3.2	-	5.0	≥5	-	1-3
Glaucoma	<2	-	-	-	-	-
Hot flashes	-	<1	-	-	-	-
Hypersensitivity reaction	-	-	-	✔	-	✔
Infection	2.8-10.3	-	16	≥5	-	-
Lupus erythematosus-like syndrome	-	-	✔	-	✔	-
Malaise	<2	<1	✔	-	✔	-
Ophthalmoplegia	-	-	✔	-	✔	-
Parosmia	<2	≤0.1	-	-	-	-
Photosensitivity reaction	<2	-	✔	-	-	-
Refraction disorder	<2	-	-	-	-	-
Stevens-Johnson syndrome	✔	-	✔	-	✔	-
Taste disturbance	<2	≤0.1	-	-	-	-
Tinnitus	<2	1-2	-	-	-	-
Toxic epidermal necrolysis	✔	-	✔	-	✔	-

Adverse Event	Atorvastatin	Amlodipine	Lovastatin	Niacin ER	Simvastatin	Ezetimibe
Visual disturbance	-	≤0.1	✔	-	-	-
Weight gain	-	<1	-	-	-	-

ER=extended-release
✔ Percent not specified
-Event not reported or incedance <1%

VII. Dosing and Administration

The usual dosing regimens for the combination HMG-CoA reductase inhibitors (statins) are summarized in Table 10. The combination statins are dosed once daily in the evening. Atorvastatin is the exception; it can be administered at any time of the day. The dosing and administration schedule of the combination products is not significantly different from that of the individual components.

Table 10. Usual Dosing for the Combination HMG-CoA Reductase Inhibitors [5-11,19-25]

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
Amlodipine/ atorvastatin*	Hypercholesterolemia; heterozygous familial/nonfamilial hypercholesterolemia; secondary prevention of cardiovascular events: Tablet: atorvastatin: initial, 10-20 mg once daily; maximum, 80 mg daily. For low-density lipoprotein cholesterol (LDL-C) reduction >45%, initiate at 40 mg once daily. Primary prevention of cardiovascular events: Tablet: atorvastatin: initial, 10 mg once daily Homozygous familial hypercholesterolemia: Tablet: atorvastatin: initial, 10 mg once daily; maximum, 80 mg daily Hypertriglyceridemia: Tablet: atorvastatin: initial, 10 mg once daily; maximum, 80 mg daily Hypertension/angina Tablet: amlodipine: initial, 2.5-5 mg once daily; maximum, 10 mg daily	Heterozygous familial hypercholesterolemia (Adolescents 10-17 years old): Tablet: atorvastatin: initial, 10 mg once daily; maximum, 20 mg daily (doses greater than 20 mg have not been studied in this patient population) Safety and efficacy of atorvastatin in children younger than 10 years of age have not been established. Hypertension (Adolescents 6-17 years): Tablet: amlodipine, 2.5-5 mg once daily Safety and efficacy of doses above 5 mg daily of amlodipine have not been established in children. Note: there have been no studies conducted to determine the safety or effectiveness of Caduet® in pediatric populations.	Tablets: 2.5/10 mg 2.5/20 mg 2.5/40 mg 5/10 mg 5/20 mg 5/40 mg 5/80 mg 10/10 mg 10/20 mg 10/40 mg 10/80 mg
Niacin ER/ lovastatin†	Tablet: initial, 500/20 mg once daily at bedtime; may titrate up by up to 500 mg daily every 4 weeks; maximum, 2,000/40 mg daily	Safety and efficacy in children have not been established.	Tablets: 500/20 mg 750/20 mg 1,000/20 mg 1,000/40 mg
Ezetimibe/ simvastatin‡	Primary hypercholesterolemia: Tablet: initial, 10/20 mg once daily at bedtime, or 10/10 mg in patients requiring less aggressive LDL-C lowering, or 10/40 mg in patients requiring LDL-C lowering >55% Homozygous familial hypercholesterolemia:	Safety and efficacy in children have not been established.	Tablets: 10/10 mg 10/20 mg 10/40 mg 10/80 mg

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
	Tablet: 10/40-10/80 mg once daily at bedtime		

* Small, fragile or elderly individuals or patients with hepatic insufficiency may be started on 2.5 mg amlodipine daily.
† Equivalent doses of lovastatin-niacin can be substituted for Niaspan® but should not be substituted for other modified-release niacin products.
‡Product should not be started in those with severe renal insufficiency unless the patient has already tolerated treatment with simvastatin ≥5 mg.

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the combination HMG-CoA reductase inhibitors (statins) are summarized in Table 11.

Table 11. Comparative Clinical Trials Using the Combination HMG-CoA Reductase Inhibitors

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Hypercholesterolemia, Primary				
Preston et al[26] RESPOND Atorvastatin-amlodipine 5 mg/10 mg once daily, separate entities vs atorvastatin-amlodipine 10 mg/10 mg once daily, separate entities vs atorvastatin-amlodipine 5 mg/20 mg once daily, separate entities vs atorvastatin-amlodipine 10 mg/20 mg once daily, separate entities vs atorvastatin-amlodipine	DB, RCT Patients 18-75 years of age with hypertension (HTN) and dyslipidemia	N=1,660 8 weeks	Primary: Mean change from baseline in systolic blood pressure (SBP), diastolic blood pressure (DBP), and reduction of LDL-C Secondary: Augmentation of blood pressure-lowering with the addition of atorvastatin and augmentation of LDL-C-lowering with the addition of amlodipine, reduction in the Framingham risk scores, adverse effects	Primary: Regardless of dose, combination therapy with atorvastatin and amlodipine was associated with greater reduction in SBP from baseline compared to atorvastatin alone (P<0.001). Regardless of dose, combination therapy with atorvastatin and amlodipine was associated with greater reduction in LDL-C from baseline compared to amlodipine alone (P<0.001). Secondary: Regardless of dose, there was no significant difference in terms of SBP-lowering from baseline between patients taking atorvastatin and amlodipine and those on amlodipine monotherapy (P>0.05). Regardless of dose, there was no significant difference in terms of LDL-C-lowering from baseline between patients taking atorvastatin and amlodipine and those on atorvastatin monotherapy (P>0.05). Atorvastatin-amlodipine 5/10 mg once daily was more effective in reducing baseline LDL-C level compared to atorvastatin monotherapy (P=0.007). A maximal reduction in the Framingham risk scores was observed in the atorvastatin-amlodipine 5/80 mg and atorvastatin-amlodipine 10/80 mg treatment groups (P value not reported). The proportion of patients who discontinued therapy due to adverse effects was similar in the combination, amlodipine, and atorvastatin groups (5.6% vs 5.4% vs 4.1, respectively; P value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
5 mg/40 mg once daily, separate entities vs atorvastatin-amlodipine 10 mg/40 mg once daily, separate entities vs atorvastatin-amlodipine 5 mg/80 mg once daily, separate entities vs atorvastatin-amlodipine 10 mg/80 mg once daily, separate entities vs amlodipine 5 mg or 10 mg once daily vs atorvastatin 10 mg, 20 mg, 40 mg, or 80 mg once daily vs placebo				
Flack et al[27]	MC, OL	N=489	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
CAPABLE Atorvastatin-amlodipine 5 mg/10 mg daily, combination entity vs atorvastatin-amlodipine 5 mg/20 mg daily, combination entity vs atorvastatin-amlodipine 5 mg/40 mg daily, combination entity vs atorvastatin-amlodipine 5 mg/80 mg daily, combination entity vs atorvastatin-amlodipine 10 mg/10 mg daily, combination entity vs atorvastatin-amlodipine 10 mg/20 mg daily, separate	African-Americans 18-80 years of age with uncontrolled HTN and dyslipidemia; patients were excluded if their blood pressure was at goal or if they were receiving both amlodipine and atorvastatin, maximum-dose calcium channel blocker, or 80 mg of atorvastatin (with LDL-C ≥100 mg/dL), were pregnant/lactating, had impaired renal or hepatic function, MI within 6 months, coronary revascularization, atherosclerotic stroke, or transient ischemic attack within 3 months, a history of cardiomyopathy or chronic heart failure, secondary HTN or secondary dyslipidemia	20 weeks	Proportion of patients in 3 cardiovascular risk groups (group 1: patients without additional risk factors; group 2: patients with >1 additional risk factors, excluding CHD and diabetes; group 3: patients with CHD or CHD risk equivalent) who reached both their JNC 7 and NCEP ATP III goals at end point Secondary: Change from baseline in SBP and DBP, LDL-C, total cholesterol, triglycerides, HDL-C, apolipoprotein B	More patients in groups 1 and 2 had reached both their JNC 7 and NCEP ATP III goals at end point compared to the group-3 patients (69.7%, 66.7%, and 28.2%, respectively; *P* value not reported). Secondary: Atorvastatin-amlodipine therapy was associated with a 17.5 mm Hg and 10.1 mm Hg decrease in the SBP and DBP from baseline, respectively (*P* value not reported). Atorvastatin-amlodipine therapy was associated with a 23.6% reduction in LDL-C from baseline (*P* value not reported). Atorvastatin-amlodipine therapy was associated with a 17% reduction in total cholesterol from baseline (*P* value not reported). Atorvastatin-amlodipine therapy was associated with a 2.2% increase in HDL-C from baseline (*P* value not reported). Atorvastatin-amlodipine therapy was associated with a 6.9% reduction in TG from baseline (*P* value not reported). Atorvastatin-amlodipine therapy was associated with a 19.3% reduction in apo B from baseline (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
entities vs atorvastatin-amlodipine 10 mg/40 mg daily, combination entity vs atorvastatin-amlodipine 10 mg/80 mg daily, combination entity				
Messerli et al[28] AVALON Amlodipine 5 mg daily for 8 weeks, followed by the addition of atorvastatin 10 mg for another 8 weeks, followed by a 12-week open-label treatment vs atorvastatin 10 mg daily for 8 weeks, followed by the addition of amlodipine 5 mg for another 8 weeks, followed by a 12-week open-label treatment vs	DD, MC, OL, RCT Patients with HTN and dyslipidemia	N=847 28 weeks	Primary: Proportion of patients who reached both their JNC 7 and NCEP ATP III goals, side effects Secondary: Not reported	Primary: More patients in the combination group reached both their JNC 7 and NCEP ATP III LDL-C goals at 8 weeks compared to patients receiving amlodipine or atorvastatin as monotherapy (45%, 8.3%, and 28.6%, respectively; $P<0.001$). The incidence of side effects was similar across all treatment groups (P value not reported). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
atorvastatin-amlodipine 5 mg/10 mg daily for 16 weeks, followed by a 12-week open-label treatment vs placebo daily for 16 weeks, followed by a 12-week open-label treatment				
Sharma et al[29] Niacin ER/lovastatin 1,500 mg/20 mg daily, combination entity, titrated up to LDL-C goal	MC, I, OL Patients living in India with HTN and dyslipidemia	N=131 24 weeks	Primary: Percent change from baseline in LDL-C, HDL-C, TG, total cholesterol Secondary: Not reported	Primary: Niacin ER/lovastatin therapy was associated with a statistically significant reduction from baseline in LDL-C (38%), TG (21%), and total cholesterol (25.2%) at week 24 of therapy (P<0.01). Niacin ER/lovastatin therapy was associated with a statistically significant increase from baseline in HDL-C at week 24 of therapy (18.2%; P<0.01). Secondary: Not reported
Advicor Package Insert Study[8] Niacin ER/lovastatin (Advicor®) 2,000 mg/40 mg daily, combination entity vs niacin ER (Niaspan®) daily vs lovastatin 40 mg daily	DB, MC, RCT Patients with type IIa and IIb hyperlipidemia	N=179 28 weeks	Primary: Mean percent change from baseline in LDL-C Secondary: Mean percent change from baseline in HDL-C, TG	Primary: At 28 weeks, niacin ER/lovastatin combination therapy arm was associated with a significant reduction in LDL-C from baseline compared with niacin ER and lovastatin 40 mg monotherapy groups (42%, 14%, and 32%, respectively; P<0.0001). Secondary: At 28 weeks, niacin ER/lovastatin combination therapy arm was associated with a significant increase in HDL-C from baseline compared with niacin ER and lovastatin 40 mg monotherapy groups (30%, 24%, and 6%, respectively; P value not reported). At 28 weeks, niacin ER/lovastatin combination therapy arm was associated with a significant reduction in TG from baseline

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				compared with niacin ER and lovastatin 40 mg monotherapy groups (44%, 31%, and 20%, respectively; *P* value not reported).
Bays, Du jovne et al[30] ADVOCATE Niacin ER/lovastatin 1,000 mg/40 mg daily, combination entity vs niacin ER/lovastatin 2,000 mg/40 mg daily, combination entity vs simvastatin 40 mg daily vs atorvastatin 40 mg daily	MC, OL, R Patients 18-70 years old, with 2 consecutive LDL-C ≥160 mg/dL (if no CAD), or ≥130 mg/dL (with CAD), TG <300 mg/dL, and HDL-C <45 mg/dL (men) or <50 mg/dL (women); patients were excluded if they had an allergy to any of the study drugs, a history of substance abuse or dependence within 12 months, consumption of >14 alcoholic drinks/week, uncontrolled psychiatric disease, active gallbladder disease, uncontrolled HTN, renal insufficiency, hepatic dysfunction, heart failure NYHA class III/IV, active gout symptoms or uric acid >1.3 times the ULN, active peptic ulcer disease, type 1 or 2 diabetes, fibromyalgia,	N=315 16 weeks	Primary: Percent change from baseline in LDL-C and HDL-C Secondary: Percent change from baseline in total cholesterol, apo B, apo AI, HDL subfractions, HDL_2 and HDL_3 and median percent change in TG and lipoprotein(a)	Primary: Atorvastatin was associated with a statistically significant 49% reduction in LDL-C from baseline at week-16 of therapy, compared with a 39%, 42%, and 39% reduction observed with niacin ER/lovastatin 1,000/40 mg, niacin ER/lovastatin 2,000/40 mg, and simvastatin groups, respectively ($P \leq 0.05$). Niacin ER/lovastatin 1,000/40 mg and 2,000/40 mg therapies were associated with a statistically significant increase in HDL-C from baseline at week 16 of therapy, compared with atorvastatin and simvastatin groups (17%, 32%, 6%, and 7%, respectively; $P \leq 0.05$). Secondary: Niacin ER/lovastatin 1,000/40 mg, niacin ER/lovastatin 2,000/40 mg, and atorvastatin groups experienced a statistically significant reduction in TG from baseline at week 16 of therapy, compared with the simvastatin group (29%, 49%, 31%, and 19%, respectively; $P \leq 0.05$). Niacin ER/lovastatin 1,000/40 mg and 2,000/40 mg therapies were associated with a statistically significant reduction in lipoprotein(a) from baseline at week 16 of therapy, compared with atorvastatin and simvastatin groups (19%, 21%, 0%, and 2%, respectively; $P \leq 0.05$). Niacin ER/lovastatin 1,000/40 mg, niacin ER/lovastatin 2,000/40 mg, and simvastatin groups were associated with a statistically significant increase in apo AI from baseline at week-16 of therapy, compared with the atorvastatin group (7%, 14%, 6%, and 2%, respectively; $P < 0.05$). Niacin ER/lovastatin 2,000/40 mg and atorvastatin were associated with a statistically significant reduction in lipoprotein B from baseline at week 16 of therapy, compared with the niacin

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	cancer within the previous 5 years, unstable angina, MI, CABG, stroke, or percutaneous coronary angioplasty within 6 months			ER/lovastatin 2,000/40 and simvastatin groups (38%, 40%, 33%, and 31%, respectively; *P*<0.05). Niacin ER/lovastatin 1,000/40 mg, and niacin ER/lovastatin 2,000/40 mg were associated with a statistically significant increase in HDL_2 and HDL_3 from baseline at week 16 of therapy, compared with the atorvastatin and simvastatin groups (*P*<0.05).
McKenney et al[31] COMPELL Atorvastatin 20 mg for the first 8 weeks, titrated up to 40 mg on weeks 9-12 in addition to niacin ER 500 mg for the first 4 weeks, titrated up to 1,000 mg on weeks 5-8, and 2,000 mg on weeks 9-12 vs simvastatin 20 mg for the first 8 weeks, titrated up to 40 mg on weeks 9-12 in addition to ezetimibe 10 mg for 12 weeks vs rosuvastatin 10 mg for the first 8 weeks, titrated up to 20 mg on weeks 9-12, in addition to niacin ER 500 mg for the first 4 weeks,	MC, OL, PG, RCT Adult patients ≥21 years of age with hypercholesterolemia eligible for treatment based on the NCEP ATP III guidelines, with two consecutive LDL-C levels within 15% of each other and mean TG ≤300 mg/dL; patients were excluded if they had secondary dyslipidemia, known hypersensitivity to the study drugs, major organ system disease, severe HTN, diabetes, major cardiovascular event within 12 months, severe heart failure, history of myopathy, active gout, life expectancy <2 years, had active liver disease, creatinine clearance <30 ml/min,	N=292 12 weeks	Primary: LDL-C level at week 12 Secondary: HDL-C level at week 12, non–HDL-C, total cholesterol, TG, lipoprotein(a), apo B	Primary: Patients randomized to atorvastatin/niacin ER, rosuvastatin/niacin ER, simvastatin/ezetimibe, and rosuvastatin therapies experienced similar reductions in LDL-C from baseline at week 12 of the study (56%, 51%, 57%, and 53%, respectively; *P*=0.093). Secondary: Patients randomized to atorvastatin/niacin ER experienced a statistically significant reduction in apo B from baseline at week 12 of the study compared to the rosuvastatin group (43% vs 39%, respectively; *P*≤0.05). Patients randomized to atorvastatin/niacin ER experienced a statistically significant increase in HDL-C from baseline at week 12 of the study compared to the simvastatin/ezetimibe and rosuvastatin groups (22%, 10%, and 7%, respectively; *P*≤0.05). Patients randomized to atorvastatin/niacin ER experienced a statistically significant reduction in TG from baseline at week 12 of the study compared to the simvastatin/ezetimibe and rosuvastatin groups (47%, 33%, and 25%, respectively; *P*≤0.05). Patients randomized to atorvastatin/niacin ER experienced a statistically significant reduction in lipoprotein(a) from baseline at week 12 of the study compared to the simvastatin/ezetimibe and rosuvastatin groups (14%, –7%, and –18%, respectively; *P*≤0.05). Side effects were similar across treatment groups (*P* value not

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
titrated up to 1,000 mg on weeks 5-12 vs rosuvastatin 10 mg for the first 4 weeks, titrated up to 20 mg on weeks 5-8, and 40 mg on weeks 9-12	or uric acid > three times the ULN			reported). There were no cases of myopathy or hepatotoxicity reported during the study period.
Rodney et al[32] Ezetimibe 10 mg, in addition to simvastatin 20 mg, separate entities, for 12 weeks vs simvastatin 20 mg, in addition to placebo, separate entities, for 12 weeks	DB, MC, PG, RCT African-American patients with LDL-C ≥145 mg/dL but ≤250 mg/dL, TG ≤350 mg/dL	N=247 12 weeks	Primary: Mean change from baseline in LDL-C level, total cholesterol, TG, HDL-C, non–HDL-C, apo B Secondary: Not reported	Primary: Patients on the combination therapy experienced a statistically significant LDL-C reduction from baseline compared to the simvastatin monotherapy group (45.6% vs 28.3%; *P*≤0.01). Patients on the combination therapy experienced a statistically significant reduction in total cholesterol from baseline compared to the simvastatin monotherapy group (33% vs 21%; *P*≤0.01). Patients on the combination therapy experienced a statistically significant triglyceride reduction from baseline compared to the simvastatin monotherapy group (22% vs 15%; *P*≤0.01). Patients on the combination therapy experienced a statistically significant non–HDL-C reduction from baseline compared to the simvastatin monotherapy group (42% vs 26%; *P*≤0.01). Patients on the combination therapy experienced a statistically significant apo B reduction from baseline compared to the simvastatin monotherapy group (38% vs 25%; *P*≤0.01). There was no difference in the change of HDL level from baseline between the two groups (~1-2% increase in each group; *P* value not reported). There was no statistically significant difference in side effects

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				between the combination therapy and simvastatin groups (*P* value not reported). Secondary: Not reported
Patel et al[33] Ezetimibe 10 mg, in addition to simvastatin 20 mg, separate entities, for 6 weeks vs simvastatin 20 mg, in addition to placebo, separate entities, for 6 weeks	DB, MC, PG, RCT Patients 18-75 years of age with primary hypercholesterolemia and CHD (at least 3 month prior to baseline), not on lipid management therapy; patients were excluded if they were women on hormonal therapy, taking statins within 6 weeks, potent CYP3A4 inhibitors within 5 weeks, oral corticosteroids started within 6 weeks or verapamil within 4 days of study onset, had ALT/AST or CK >1.5 times the ULN, poorly controlled, newly diagnosed diabetes type 1 or 2, or had changed their antidiabetic therapy within 3 months of baseline, had uncontrolled HTN, or	N=153 6 weeks	Primary: Mean change from baseline in LDL-C level, proportion of patients who reached LDL-C target (<3 mmol/L) at 6 weeks Secondary: Change in serum cholesterol, TG, HDL	Primary: Patients on the combination therapy experienced an additional LDL-C reduction of 14.6% compared to the simvastatin monotherapy group (95% CI, 10.1 to 19.1; *P*<0.0001). A significantly greater proportion of patients randomized to the combination therapy achieved their LDL-C goal compared to the monotherapy group (93% vs 75%, respectively; *P*<0.001). Patients on combination therapy were 5.1 times more likely to reach target LDL-C levels compared to patients on simvastatin alone (95% CI, 1.8 to 15.0; *P*=0.003). Secondary: Patients on the combination therapy experienced an additional total cholesterol reduction of 0.69 mmol/L compared to the simvastatin group (95% CI, 0.48 to 0.90; *P*<0.0001). Significantly greater proportion of patients in the combination therapy group reached total cholesterol target (<4 mmol/l) compared to simvastatin group (*P*<0.001). Greater reduction in TG was observed in the combination therapy group compared to the simvastatin group (20.4% vs 12.4%; *P*=0.06). There was no difference in the change of HDL level from baseline between the two groups (~6% increase in each group; *P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	body mass index ≥30 kg/m^2			There was no statistically significant difference in treatment emergent adverse events between the combination therapy and simvastatin groups (40% vs 25%; *P*=0.07).
Masana et al[34] Ezetimibe 10 mg daily, in addition to simvastatin 10 mg titrated up to 80 mg daily, separate entities vs simvastatin 10 mg titrated up to 80 mg daily, in addition to placebo, separate entities	DB, ES, MC, RCT Patients with primary hypercholesterolemia ≥18 years of age, currently taking a stable daily dose of a statin ≥6 weeks, with LDL-C above the NCEP ATP II guideline target level, TG <350 mg/dL; patients were excluded if they had heart failure, uncontrolled cardiac arrhythmias, MI, CABG, coronary angioplasty, or severe peripheral artery disease within the past 3 months, unstable angina pectoris, poorly controlled or newly diagnosed diabetes, uncontrolled endocrine or metabolic disease, impaired renal function, active or chronic liver or hepatobiliary disease, ALT or AST >2 times the ULN, creatine	N=355 48 weeks	Primary: Percent change from baseline in LDL-C between the study groups at week 12 Secondary: Percent change from baseline in total cholesterol, TG, HDL-C, non–HDL-C, the ratios of LDL-C:HDL-C and TC:HDL-C at 12 weeks	Primary: At week 12, simvastatin-ezetimibe groups experienced a statistically significant 27% reduction in LDL-C compared to patients on simvastatin monotherapy (*P*<0.001). The benefit was maintained up to week 48 of the study (*P* value not reported). Secondary: At week 12, simvastatin-ezetimibe groups experienced a statistically significant reduction in total cholesterol, TG, non–HDL-C, ratios of LDL-C:HDL-C, and TC:HDL-C, compared to patients on simvastatin monotherapy (*P*<0.001). At week 12, simvastatin-ezetimibe groups experienced a non-significant 2.6% increase in HDL-C compared to patients on simvastatin monotherapy (*P*=0.07). Treatment-related adverse effects were similar in simvastatin and simvastatin-ezetimibe groups (17% and 19%, respectively; *P* value not reported). There were no cases of rhabdomyolysis or myopathy during the study.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	phosphokinase >1.5 times the ULN, and cancer (other than basal cell carcinoma) within the past 5 years			
Denke et al[35] EASE Ezetimibe 10 mg, in addition to ongoing statin therapy for 6 weeks, separate entities vs placebo, in addition to ongoing statin therapy for 6 weeks, separate entities	DB, MC, PG, RCT Adult patients with hypercholesterolemia, with LDL-C levels exceeding the NCEP ATP goals, on an approved dose of a statin for 6 weeks prior to study entry, following a cholesterol-lowering diet; patients were excluded if within 3 months of study entry had an acute coronary insufficiency, MI, stroke, surgical coronary intervention, or other major vascular surgery procedures, untreated hypothyroidism or hyperthyroidism, untreated uncontrolled HTN, impaired renal function, active liver disease, a history of statin-induced myopathy,	N=3,030 6 weeks	Primary: Mean change from baseline in LDL-C level, proportion of patients who reached LDL-C target, change in serum cholesterol, TG, HDL in patients with diabetes, metabolic syndrome or neither Secondary: Not reported	Primary: The addition of ezetimibe to ongoing statin therapy, as compared to the addition of placebo to ongoing statin therapy, was associated with an additional LDL-C reduction of 24.8% (diabetic patients), 21.4% (metabolic syndrome patients), and 22.4% (neither) from baseline ($P<0.001$). The addition of ezetimibe to ongoing statin therapy, as compared to the addition of placebo to ongoing statin therapy, was associated with an additional triglyceride reduction of 12.3% (diabetic patients), 10.7% (metabolic syndrome patients), and 11% (neither) from baseline ($P<0.001$). The addition of ezetimibe to ongoing statin therapy, as compared to the addition of placebo to ongoing statin therapy, was associated with an additional increase in HDL cholesterol among diabetic patients ($P<0.001$) and patients with metabolic syndrome ($P=0.002$) from baseline. The addition of ezetimibe to ongoing statin therapy, as compared to the addition of placebo to ongoing statin therapy, was associated with an additional non-HDL cholesterol reduction of 21.8% (diabetic patients), 19.5% (metabolic syndrome patients), and 20.3% (neither) from baseline ($P<0.001$). The addition of ezetimibe to ongoing statin therapy, as compared to the addition of placebo to ongoing statin therapy, was associated with an additional reduction in total cholesterol of 16% (diabetic patients), 14.8% (metabolic syndrome patients), and 15% (neither) from baseline ($P<0.001$).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	uncontrolled diabetes, or were taking lipid-altering medications,other than statins, or oral corticosteroids			The addition of ezetimibe to ongoing statin therapy, as compared to the addition of placebo to ongoing statin therapy, was associated with an additional reduction in apo B to apo AI ratio of 17.7% (diabetic patients), 16.6% (metabolic syndrome patients), and 15.1% (neither) from baseline (P<0.001). The addition of ezetimibe to ongoing statin therapy, as compared to the addition of placebo to ongoing statin therapy, was associated with an additional reduction from baseline in CRP of 14.8% and 9.7% among diabetic patients (P<0.001) and patients with metabolic syndrome (P=0.027), respectively. A significantly greater proportion of patients randomized to the ezetimibe combination therapy achieved their NCEP-ATP LDL-C goals compared to the control group (P<0.001). Side effects were similar across all treatment groups (P value not reported). Secondary: Not reported
Pearson et al[36] EASE Ezetimibe 10 mg, in addition to ongoing statin therapy for 6 weeks, separate entities vs placebo, in addition to ongoing statin therapy for 6	DB, MC, PG, RCT Subanalysis of the EASE study; patients > 65 years old with hypercholesterolemia, with LDL-C levels exceeding the NCEP ATP goals, on an approved dose of a statin for 6 weeks prior to study entry, following a	N=3,030 6 weeks	Primary: Mean change from baseline in LDL-C level, proportion of patients who reached LDL-C target across different races and ethnicities, change in serum cholesterol, TG, HDL at 6 weeks Secondary: Not reported	Primary: Compared to placebo, patients on the ezetimibe combination therapy experienced an LDL-C reduction of 23% (white patients), 23% (African American patients), and 21% (Hispanic patients) from baseline (P<0.001). The difference in LDL-C lowering among the three races studied was not statistically significant (P>0.5). A significantly greater proportion of patients randomized to the ezetimibe combination therapy achieved their NCEP ATP LDL-C goal compared to the control group (P<0.001). Patients on the ezetimibe combination therapy experienced a total cholesterol reduction of 15.3 mg/dL from baseline compared to the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
weeks, separate entities	cholesterol-lowering diet (for above for exclusion criteria)			control group (*P*<0.001). Patients on the ezetimibe combination therapy experienced a triglyceride reduction of 11.5 mg/dL from baseline compared to the control group (*P*<0.001). Patients on the ezetimibe combination therapy experienced an increase in HDL of 2.1 mg/dL from baseline when compared to the control group (*P*<0.001). Side effects were similar across treatment groups and races (*P* value not reported). Secondary: Not reported
Chenot et al[37] Simvastatin 40 mg daily vs ezetimibe 10 mg daily added to simvastatin 40 mg daily, separate entities vs no lipid-lowering therapy	RCT Patients admitted for an AMI (with or without ST-segment elevation) to the coronary unit, with pain that started within 24 hours of admission; patients were excluded if they had a thyroid disorder, inflammatory disease, neoplasia, serious hepatic disease, creatinine level >1.7 mg/dL, creatinine clearance <30 mL/min, CK >3 times the ULN, LDL-C <90 mg/dL, or were receiving potent	N=60 7 days	Primary: Change from baseline in LDL-C at days 2, 4 and 7, and the achievement of LDL-C <70 mg/dL Secondary: Not reported	Primary: Patients on the simvastatin-ezetimibe combination therapy experienced a statistically significant LDL-C reduction from baseline on days 2, 4, and 7 (27%, 41%, and 51%, respectively; *P*<0.001). Patients on the simvastatin monotherapy experienced a statistically significant LDL-C reduction from baseline on days 2, 4, and 7 (15%, 27%, and 25%, respectively; *P*<0.001). There was no statistically significant change from baseline in LDL-C in the no lipid-lowering therapy group (*P*≥0.09). Patients on the simvastatin-ezetimibe combination therapy achieved lower LDL-C levels compared to the simvastatin monotherapy group at day 4 (*P*=0.03) and day 7 (*P*=0.002) of the study. A greater proportion of patients randomized to the simvastatin-ezetimibe combination therapy achieved LDL-C <70 mg/dL, compared to the simvastatin monotherapy group at day 4 and day 7

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	3A4 inhibitors			(45% vs 5%, and 55% vs 10%, respectively; *P* value not reported). Secondary: Not reported
Sampalis et al[38] Ezetimibe 10 mg, in addition to ongoing statin therapy for 6 weeks, separate entities vs placebo, in addition to ongoing statin therapy for 6 weeks, separate entities	SA Adult patients with hypercholesterolemia, with LDL-C levels exceeding the NCEP ATP goals on statin therapy	N=825 6 weeks	Primary: Reduction in the 10-year risk of CAD after 6 weeks Secondary: Not reported	Primary: The addition of ezetimibe to ongoing statin therapy was associated with a 25.3% reduction in the 10-year risk of CAD (*P*<0.001). Secondary: Not reported
Gaudiani et al[39] Simvastatin 20 mg daily for 6 weeks, followed by the addition of ezetimibe 10 mg daily for another 24 weeks, separate entities vs simvastatin 20 mg daily for 6 weeks, titrated up to 40 mg daily for another 24 weeks, separate entities	DB, MC, PG, RCT Patients 30-75 years of age with type 2 diabetes (hemoglobin A_{1C} ≤9%), treated with a stable dose of pioglitazone (15-45 mg daily) or rosiglitazone (2-8 mg daily) for at least 3 months, LDL-C >100 mg/dL and TG <600 mg/dL (if already on a statin therapy); patients were excluded if they had type 1 diabetes, type I or type V hyperlipidaemia, homozygous familial	N=214 30 weeks	Primary: Percent change in LDL-C from baseline Secondary: Percent change from baseline in total cholesterol, TG, HDL-C, the ratios of LDL-C:HDL-C and TC:HDL-C, non–HDL-C, apo B, apo AI	Primary: LDL-C was reduced more by the addition of ezetimibe 10 mg to simvastatin 20 mg than by doubling the dose of simvastatin 20 mg (20.8% vs 0.3%; *P*<0.001). Secondary: Total cholesterol was reduced more by the addition of ezetimibe 10 mg to simvastatin 20 mg than by doubling the dose of simvastatin 20 mg (14.5% vs 1.5%; *P*<0.001). Non–HDL-C was reduced more by the addition of ezetimibe 10 mg to simvastatin 20 mg than by doubling the dose of simvastatin 20 mg (20% vs 1.7%; *P*<0.001). Apo B was reduced more by the addition of ezetimibe 10 mg to simvastatin 20 mg than by doubling the dose of simvastatin 20 mg (14.1% vs 1.8%; *P*<0.001). The ratios of LDL-C:HDL-C, TC:HDL-C, and apo B to apo AI

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	hypercholesterolemia, a history of active liver disease, uncontrolled HTN, renal dysfunction, hyperlipidemic pancreatitis, or hypercholesterolemia secondary to hypothyroidism, MI, percutaneous coronary angioplasty, stent insertion, CABG, or stroke within 3 months, and liver transaminase levels >30% above the ULN, CK >50% above the ULN, fasting plasma C-peptide ≤0.5 ng/mL, or if they were taking warfarin, cyclical sex hormones, or any potent inhibitors of CYP3A4			were reduced more by the addition of ezetimibe 10 mg to simvastatin 20 mg than by doubling the dose of simvastatin 20 mg (*P*<0.001). The reduction in HDL-C was similar in the simvastatin 40 mg and simvastatin-ezetimibe 10/20 mg groups (*P*=948). The incidence of treatment-related adverse effects was lower in the simvastatin 40 mg group than in the simvastatin-ezetimibe 10/20 mg group (10% and 18.3%, respectively; *P* value not reported).
Feldman, Koren et al[40] Simvastatin 10 mg daily, in addition to ezetimibe 10 mg daily for 23 weeks, separate entities vs simvastatin 20 mg daily, in	DB, MC, RCT Patients 18-80 years of age with CHD or CHD risk equivalent disease and LDL-C ≥130 mg/dL and TG ≤350 mg/dL, not pregnant, liver transaminase and CK ≤50% above the	N=710 23 weeks	Primary: LDL-C <100 mg/dL at week 5 Secondary: LDL-C <100 mg/dL at study end	Primary: Significantly more patients on the simvastatin-ezetimibe combination therapy, regardless of the dose, achieved an LDL-C level <100 mg/dL at week 5, compared with patients receiving simvastatin 20 mg monotherapy (*P*<0.001). Secondary: Significantly more patients on the simvastatin-ezetimibe combination therapy, regardless of the dose, achieved an LDL-C level <100 mg/dL at week 23, compared with patients receiving

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
addition to ezetimibe 10 mg daily for 23 weeks, separate entities vs simvastatin 40 mg daily, in addition to ezetimibe 10 mg daily for 23 weeks, separate entities vs simvastatin 20 mg daily for 23 weeks	ULN, off all lipid-lowering agents ≥6 weeks			simvastatin 20 mg monotherapy (P<0.001). At week 5, there was a statistically significant reduction in total cholesterol, non–HDL-C, apo B, ratios of TC:HDL-C, and LDL-C:HDL-C among patients randomized to the simvastatin-ezetimibe combination therapy, regardless of the dose, compared with patients receiving simvastatin 20 mg monotherapy (P<0.001). HDL-C was significantly increased only in the simvastatin-ezetimibe 10/20 mg group from baseline, compared with simvastatin monotherapy (P<0.05). At week 5, there was a statistically significant reduction in TG among patients randomized to the simvastatin-ezetimibe combination therapy, regardless of the dose, compared with patients receiving simvastatin 20 mg monotherapy (P<0.05). Treatment-related adverse effects were similar in simvastatin and simvastatin-ezetimibe 10/10 mg, 10/20 mg, 10/40 mg groups (7.5%, 9.6%, 14%, and 10%, respectively; P value not reported).
Bays, Ose et al[41] Simvastatin-ezetimibe 10 mg/10 mg daily for 12 weeks, combination product vs simvastatin-ezetimibe 10 mg/20 mg daily for 12 weeks, combination product vs simvastatin-ezetimibe	DB, MC, RCT Patients aged 18 to 80 years with primary hypercholes-terolemia, LDL-C >145 mg/dL but ≤150 mg/dL and TG ≤350 mg/dL; patients were excluded if they had an active liver disease and CK >1.5 times the ULN	N=1,528 24 weeks	Primary: Percent change in LDL-C from baseline to the end of treatment period for pooled ezetimibe/simvastatin vs simvastatin or ezetimibe monotherapy Secondary: Change and percent change from baseline in total cholesterol, TG, HDL-C, the ratios of LDL-C:HDL-C and	Primary: Averaged across all doses, simvastatin-ezetimibe combination therapy was associated with a significant reduction in LDL-C from baseline at 12 weeks, compared with simvastatin monotherapy (53% vs 39%; P<0.001). Averaged across all doses, simvastatin-ezetimibe combination therapy was associated with a significant reduction in LDL-C from baseline at 12 weeks, compared with ezetimibe monotherapy (53% vs 18.9%; P<0.001). Secondary: At each corresponding dose of simvastatin, simvastatin-ezetimibe combination therapy was associated with a significant reduction in LDL-C from baseline at 12 weeks (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
10 mg/40 mg daily for 12 weeks, combination product vs simvastatin-ezetimibe 10 mg/80 mg daily for 12 weeks, combination product vs simvastatin 10 mg daily for 12 weeks vs simvastatin 20 mg daily for 12 weeks vs simvastatin 40 mg daily for 12 weeks vs simvastatin 80 mg daily for 12 weeks vs ezetimibe 10 mg daily for 12 weeks vs			TC:HDL-C, non–HDL-C, apo B, apo AI, and C-reactive protein (CRP), proportion of patients reaching their NCEP ATP III LDL-C goal of <130 mg/dL, <100 mg/dL, or <70 mg/dL at 12 weeks	Simvastatin-ezetimibe combination therapy was associated with a significant reduction in LDL-C from baseline at 12 weeks, compared with the next highest dose of simvastatin (P<0.001). Averaged across all doses, simvastatin-ezetimibe combination resulted in a greater proportion of patients reaching their NCEP ATP III LDL-C goal of <130 mg/dL, <100 mg/dL, or <70 mg/dL at 12 weeks, compared with simvastatin (92.2%, 78.6%, 38.7% vs 79.2%, 45.9%, and 7.0%, respectively; P<0.001). Averaged across all doses, simvastatin-ezetimibe combination therapy was associated with a significant reduction in total cholesterol, TG, the ratios of LDL-C:HDL-C and TC:HDL-C, non–HDL-C, apo B, and CRP from baseline at 12 weeks, compared with simvastatin monotherapy (P<0.001). Averaged across all doses, simvastatin-ezetimibe combination therapy was not associated with a statistically significant change from baseline in HDL-C level, compared with simvastatin monotherapy (P=0.607). Treatment-related adverse effects were similar in the pooled simvastatin, simvastatin-ezetimibe, and ezetimibe groups, but were more frequent than placebo (14.8%, 15.1%, 12.8%, 8.1%, respectively; P value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo daily for 12 weeks				
Goldberg, Sapre et al[42] Simvastatin 10 mg daily, in addition to ezetimibe 10 mg daily for 12 weeks, separate entities vs simvastatin 20 mg daily, in addition to ezetimibe 10 mg daily for 12 weeks, separate entities vs simvastatin 40 mg daily, in addition to ezetimibe 10 mg daily for 12 weeks, separate entities vs simvastatin 80 mg daily, in addition to ezetimibe 10 mg daily for 12 weeks, separate entities vs simvastatin 10 mg daily for 12 weeks	DB, MC, RCT Patients ≥18 years of age with primary hypercholesterolemia, ALT and AST ≤2 times the ULN, no active liver disease, CK ≤1.5 times the ULN; patients were excluded if they had heart failure, uncontrolled cardiac arrhythmias, history of unstable or severe peripheral artery disease, MI, CABG, uncontrolled, newly diagnosed diabetes, or change in antidiabetic therapy within 3 month, renal dysfunction, coagulation disorder, uncontrolled HTN, were taking non-statin lipid-lowering drugs, immunosuppressants, corticosteroids, other potent inhibitors of P450 3A4 isoenzyme	N= 887 20 weeks	Primary: Mean percent change in LDL-C from baseline to the end of treatment period for pooled ezetimibe/ simvastatin vs simvastatin alone Secondary: Change and percent change from baseline in total cholesterol, TG, HDL-C, the ratios of LDL-C:HDL-C and TC:HDL-C, non–HDL-C, apo B, apo AI, and CRP, proportion of patients reaching their NCEP ATP III LDL-C goal of <130 mg/dL, or <100 mg/dL at 12 weeks	Primary: Averaged across all doses, simvastatin-ezetimibe combination therapy was associated with a significant 14.8% reduction in LDL-C from baseline at 12 weeks, compared with simvastatin monotherapy (53.2% vs 38.5%; *P*<0.001). Secondary: At each corresponding dose of simvastatin, simvastatin-ezetimibe combination therapy was associated with a significant reduction in LDL-C from baseline at 12 weeks (*P*<0.001). Simvastatin-ezetimibe combination therapy was associated with a significant reduction in LDL-C from baseline at 12 weeks, compared with the next highest dose of simvastatin (*P*<0.001). Averaged across all doses, simvastatin-ezetimibe combination therapy was associated with a significant reduction in total cholesterol, TG, the ratios of LDL-C:HDL-C and TC:HDL-C, non–HDL-C, apo B, and CRP from baseline at 12 weeks, compared with simvastatin monotherapy (*P*<0.001). Averaged across all doses, simvastatin-ezetimibe combination resulted in a greater proportion of patients reaching their NCEP ATP III LDL-C goal of <130 mg/dL, or <100 mg/dL at 12 weeks, compared with simvastatin (92% and 82% vs 82% and 43%, respectively; *P*<0.001). Averaged across all doses, simvastatin-ezetimibe combination therapy was not associated with a statistically significant change from baseline in HDL-C level, compared with simvastatin monotherapy (*P*=0.53). Treatment-related adverse effects were similar in the pooled

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs simvastatin 20 mg daily for 12 weeks vs simvastatin 40 mg daily for 12 weeks vs simvastatin 80 mg daily for 12 weeks vs ezetimibe 10 mg daily for 12 weeks vs placebo daily for 12 weeks				simvastatin and simvastatin-ezetimibe, but were more frequent than in the ezetimibe and placebo groups (13%, 14%, 9%, and 9%, respectively; *P* value not reported).
Ose et al[43] Ezetimibe 10 mg daily added to simvastatin 10 mg, 20 mg, 40 mg, or 80 mg daily, separate entities, for 14 weeks vs simvastatin 10 mg, 20 mg, 40 mg, or 80 mg daily for 14	DB, MC, RCT Patients with primary hypercholesterolemia (LDL-C between 145 mg/dL and 250 mg/dL and TG <350 mg/dL)	N=1,037 14 weeks	Primary: Change from baseline in LDL-C level, TG, total cholesterol, non-HDL, CRP, LDL:HDL cholesterol ratio, TC:HDL ratio, proportion of patients reaching LDL-C target (<100 mg/dL, or <70 mg/dL)	Primary: Across all doses, patients on the simvastatin-ezetimibe combination therapy experienced a statistically significant LDL-C reduction from baseline compared with the simvastatin monotherapy group (53.7% vs 38.8%; *P*<0.001). Across all doses, patients on the simvastatin-ezetimibe combination therapy experienced a statistically significant reduction from baseline in TG, total cholesterol, non-HDL, CRP, LDL:HDL cholesterol ratio, and TC:HDL ratio compared with the simvastatin monotherapy group (*P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
weeks vs ezetimibe 10 mg once daily for 14 weeks vs placebo once daily for 14 weeks			Secondary: Not reported	A significantly greater proportion of patients randomized to the simvastatin-ezetimibe combination therapy achieved LDL-C <100 mg/dL, compared to the simvastatin group (79.2% vs 47.9%; *P*<0.001). A greater proportion of patients randomized to the simvastatin-ezetimibe combination therapy achieved LDL-C <70 mg/dL, compared to the simvastatin group (30.4% vs 7%; *P*<0.001). The incidence of drug-related adverse effects was similar in the simvastatin-ezetimibe and simvastatin monotherapy groups (7.4% vs 5.5%, respectively; *P* value not reported). Secondary: Not reported
Davidson et al[44] Simvastatin 10 mg daily, in addition to ezetimibe 10 mg daily for 12 weeks, separate entities vs simvastatin 20 mg daily, in addition to ezetimibe 10 mg daily for 12 weeks, separate entities vs simvastatin 40 mg daily, in addition to ezetimibe 10 mg daily for 12 weeks, separate entities	DB, MC, RCT Patients >18 years of age with primary hypercholesterolemia; patients were excluded if they had heart failure, uncontrolled cardiac arrhythmias, history of unstable or severe peripheral artery disease, MI, or CABG within 6 months, uncontrolled, newly diagnosed diabetes, or change in antidiabetic therapy within 1 month, active liver disease, renal dysfunction,	N=668 20 week	Primary: Mean percent change in LDL-C from baseline to the end of treatment period Secondary: Change and percent change from baseline in total cholesterol, TG, HDL-C, the ratios of LDL-C:HDL-C and TC:HDL-C, non–HDL-C, apo B, apo AI, and CRP	Primary: Averaged across all doses, simvastatin-ezetimibe combination therapy was associated with a significant reduction in LDL-C from baseline at 12 weeks, compared with simvastatin monotherapy (49.9% vs 36.1%; *P*<0.001). Averaged across all doses, simvastatin-ezetimibe combination therapy was associated with a significant reduction in LDL-C from baseline at 12 weeks, compared with ezetimibe monotherapy (49.9% vs 18.1%; *P*<0.001). Patients randomized to either simvastatin-ezetimibe 10/10 mg or simvastatin 80 mg monotherapy experienced a 44% reduction in LDL-C from baseline at 12 weeks (*P* value not reported). Secondary: At each corresponding dose of simvastatin, simvastatin-ezetimibe combination therapy was associated with a significant reduction in LDL-C from baseline at 12 weeks (*P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs simvastatin 80 mg daily, in addition to ezetimibe 10 mg daily for 12 weeks, separate entities vs simvastatin 10 mg daily for 12 weeks vs simvastatin 20 mg daily for 12 weeks vs simvastatin 40 mg daily for 12 weeks vs simvastatin 80 mg daily for 12 weeks vs ezetimibe 10 mg daily for 12 weeks vs	coagulation disorder, unstable endocrine disease			Simvastatin-ezetimibe combination therapy was associated with a significant reduction in LDL-C from baseline at 12 weeks, compared with the next highest dose of simvastatin (P<0.01). Averaged across all doses, simvastatin-ezetimibe combination therapy was associated with a significant reduction in total cholesterol, TG, the ratios of LDL-C:HDL-C and TC:HDL-C, non–HDL-C, and apo B from baseline at 12 weeks, compared with simvastatin monotherapy (P<0.01). Averaged across all doses, simvastatin-ezetimibe combination therapy was associated with a statistically significant increase from baseline in HDL-C level, compared with simvastatin monotherapy (P=0.03). Averaged across all doses, simvastatin-ezetimibe combination therapy was associated with a significant reduction in total cholesterol, TG, the ratios of LDL-C:HDL-C and TC:HDL-C, non–HDL-C, and apo B from baseline at 12 weeks, compared with ezetimibe monotherapy (P<0.01). Averaged across all doses, simvastatin-ezetimibe combination therapy was associated with a statistically significant increase from baseline in HDL-C level, compared with ezetimibe monotherapy (P=0.02). A significantly greater proportion of patients on simvastatin-ezetimibe therapy experienced a reduction in LDL-C >50% from baseline, compared with the simvastatin monotherapy group (P value not reported). Treatment-related adverse effects were similar in the pooled simvastatin and simvastatin-ezetimibe groups (72% and 69%, respectively; P value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo daily for 12 weeks				
Feldman, Davidson et al[45] Simvastatin-ezetimibe 10 mg/10 mg daily for 12 weeks, combination product vs simvastatin-ezetimibe 10 mg/20 mg daily for 12 weeks, combination product vs simvastatin-ezetimibe 10 mg/40 mg daily for 12 weeks, combination product vs simvastatin-ezetimibe 10 mg/80 mg daily for 12 weeks, combination product vs simvastatin 10 mg daily for 12 weeks vs simvastatin 20 mg daily for 12 weeks	MA Post hoc analysis of three randomized, double-blind, placebo controlled studies among patients with primary hypercholesterolemia	N=3,083 (3 studies) 28 weeks	Primary: Percent change in LDL-C, TG, non–HDL-C, apo B, and CRP from baseline, achievement of LDL-C <100 mg/dL at week-12 among patients <65 and ≥65 years of age Secondary: Not reported	Primary: Averaged across all doses, simvastatin-ezetimibe combination therapy was associated with a significant reduction in LDL-C, TG, non–HDL-C, apo B, and CRP from baseline at 12 weeks, compared with simvastatin monotherapy (*P*<0.001). These affects did not differ between the older and younger patients (*P* value not reported). Treatment with simvastatin-ezetimibe and simvastatin monotherapy resulted in comparable increases in HDL-C from baseline (8% vs 7%, respectively; *P* value not reported). Significantly more patients, in all age groups, on the simvastatin-ezetimibe combination therapy, regardless of the dose, achieved an LDL-C level <100 mg/dL at week 12, compared with patients receiving simvastatin monotherapy (79% vs 42%; *P*<0.001). Significantly more patients, in all age groups, on the simvastatin-ezetimibe combination therapy, regardless of the dose, achieved an LDL-C level <70 mg/dL at week 12, compared with patients receiving simvastatin monotherapy (37% vs 6%; *P*<0.001). Treatment-related adverse effects were similar in simvastatin and simvastatin-ezetimibe combination therapy groups, regardless of dose used and age group (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs simvastatin 40 mg daily for 12 weeks vs simvastatin 80 mg daily for 12 weeks vs ezetimibe 10 mg daily for 12 weeks vs placebo daily for 12 weeks				
Ballantyne, Blazing et al[46] Simvastatin-ezetimibe 10 mg/20 mg, combination product, daily for weeks 1-6, titrated to simvastatin-ezetimibe 10 mg/40 mg for weeks 7-18, titrated to simvastatin-ezetimibe 10 mg/80 mg for weeks 19-24 vs simvastatin-ezetimibe 10 mg/10 mg, combination product, daily for weeks 1-6, titrated to simvastatin-	DB, MC, RCT Patients ≥18 years with a LDL-C at or above drug treatment thresholds established by NCEP ATP III guidelines, with CAD or CAD risk equivalent, or with ≥2 risk factors conferring a 10-year risk of >20% for CHD, and with LDL cholesterol ≥130 mg/dL, no CHD or its risk equivalent, and with ≥2 risk factors	N=788 24 weeks	Primary: Mean percent change in LDL-C from baseline to end of treatment period Secondary: Percent change in LDL-C and HDL-C from baseline to the ends of the second and fourth (final) 6-week treatment periods	Primary: Averaged across all doses, simvastatin-ezetimibe combination therapy was associated with a significant reduction in LDL-C from baseline, compared with atorvastatin monotherapy (52.4% vs 45.1%; *P*<0.001). Averaged across all doses, simvastatin-ezetimibe combination therapy was associated with a significant increase in HDL-C from baseline, compared with atorvastatin monotherapy (12.3% vs 6.5%; *P*<0.001). Secondary: At the end of treatment period 2, patients randomized to simvastatin-ezetimibe 10/20 mg and 10/40 mg experienced a significant reduction in LDL-C from baseline, compared with the atorvastatin 20 mg monotherapy group (50.2%, 54.3%, and 44.3%, respectively; *P*≤0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
ezetimibe 10 mg/20 mg for weeks 7-12, titrated to simvastatin-ezetimibe 10 mg/40 mg for weeks 12-18, titrated to simvastatin-ezetimibe 10 mg/80 mg for weeks 19-24 vs atorvastatin 10 mg daily for weeks 1-6, titrated to atorvastatin 20 mg for weeks 7-12, titrated to atorvastatin 40 mg for weeks 12-18, titrated to atorvastatin 80 mg for weeks 19-24	conferring a 10-year risk of <20% for CHD, and with LDL-C ≥160 mg/dL, and no CHD or its risk equivalent with <2 risk factors and with LDL-C ≥190 mg/dL, TG ≤350 mg/dL, ALT or AST <1.5 times the ULN, serum creatinine ≤1.5 mg/dL, no active liver disease, CK <1.5 times the ULN, and a hemoglobin A_{1C} <9% in patients with diabetes			At the end of treatment period 2, patients randomized to simvastatin-ezetimibe 10/40 mg experienced a significant increase in HDL-C from baseline, compared with the atorvastatin 20 mg monotherapy group (12.4% vs 6.9%; *P*≤0.05). At the end of treatment period 4, patients randomized to simvastatin-ezetimibe 10/40 mg experienced a significant reduction in LDL-C from baseline, compared with the atorvastatin 80 mg monotherapy group (59.4% vs 52.5%, respectively; *P*≤0.05). At the end of treatment period 4, patients randomized to simvastatin-ezetimibe 10/40 mg experienced a significant increase in HDL-C from baseline, compared with the atorvastatin 80 mg monotherapy group (12.3% vs 6.5%; *P*≤0.05). The safety of simvastatin-ezetimibe was observed to be similar to that of atorvastatin monotherapy (*P* value not reported).
Goldberg, Guyton et al[47] VYTAL Simvastatin-ezetimibe 10 mg/20 mg daily for 6 weeks, combination product vs simvastatin-ezetimibe 10 mg/40 mg daily for 6 weeks, combination product vs atorvastatin 10 mg daily for	DB, MC, PG, RCT Adult patients with type 2 diabetes between 18 and 80 years of age with hemoglobin A_{1c} ≤8.5%, LDL-C >100 mg/dL and a triglyceride level <400 mg/dL	N=1,229 6 weeks	Primary: Percent reduction in LDL-C level at week 6 Secondary: Proportion of patients who achieved the NCEP ATP III LDL-C goal (<70 mg/dL), proportion of patients who achieved LDL-C level of <100 mg/dL, percent change from baseline in HDL-C, non–HDL-C, total cholesterol, TG, and CRP	Primary: Patients randomized to simvastatin 20 mg/ezetimibe 10 mg therapy experienced greater reduction in LDL-C from baseline at week 6 of the study compared to patients receiving atorvastatin 10 mg or 20 mg daily (53.6%, 38.3%, and 44.6%, respectively; *P*<0.001). Patients randomized to simvastatin 40 mg/ezetimibe 10 mg therapy experienced greater reduction in LDL-C from baseline at week 6 of the study compared to patients receiving atorvastatin 40 mg daily (57.6% and 50.9%, respectively; *P*<0.001). Secondary: A greater proportion of patients randomized to simvastatin 20 mg/ezetimibe 10 mg therapy achieved LDL-C<70 mg/dL compared to patients receiving atorvastatin 10 mg or 20 mg daily (59.7%, 21.5%, and 35%, respectively; *P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
6 weeks vs atorvastatin 20 mg daily for 6 weeks vs atorvastatin 40 mg daily for 6 weeks				A greater proportion of patients randomized to simvastatin 40 mg/ezetimibe 10 mg therapy achieved LDL-C<70 mg/dL compared to patients receiving atorvastatin 40 mg daily (74.4% and 55.2%, respectively; *P*<0.001). A greater proportion of patients randomized to simvastatin 20 mg/ezetimibe 10 mg therapy achieved LDL-C<100 mg/dL compared to patients receiving atorvastatin 10 mg or 20 mg daily (90.3%, 70%, and 82.1%, respectively; *P*=0.007). A greater proportion of patients randomized to simvastatin 40 mg/ezetimibe 10 mg therapy achieved LDL-C<100 mg/dL compared to patients receiving atorvastatin 40 mg daily (93.4% and 88.8%, respectively; *P*=0.07). Patients randomized to simvastatin-ezetimibe combination therapy, at all doses, experienced a significant increase in HDL level (*P*≤0.001), a greater reduction in total cholesterol, and non-HDL cholesterol (*P*<0.001) compared to patients receiving atorvastatin, at all doses. Patients randomized to simvastatin 20 mg/ezetimibe 10 mg combination therapy experienced a significant reduction in CRP and triglyceride level compared to patients receiving atorvastatin (*P*=0.02). Side effects were similar in the simvastatin-ezetimibe and atorvastatin groups (19.85 vs 22.7%; *P* value not reported).
Ballantyne, Abate et al[48] VYVA Simvastatin-ezetimibe 10 mg/10 mg daily, combination product for 6	DB, MC, PG, RCT Adult patients with hypercholesterolemia, between 18 and 79 years of age, with an LDL-C level at or	N=1,902 10 weeks	Primary: Mean percent change from baseline in LDL-C at 6 weeks Secondary: Percent change from	Primary: Averaged across all doses, simvastatin-ezetimibe combination therapy was associated with a significant reduction in LDL-C from baseline at 6 weeks, compared with atorvastatin (53.4% vs 45.3%; *P*<0.001). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
weeks vs simvastatin-ezetimibe 10 mg/20 mg daily, combination product for 6 weeks vs simvastatin-ezetimibe 10 mg/40 mg daily, combination product for 6 weeks vs simvastatin-ezetimibe 10 mg/80 mg daily, combination product for 6 weeks vs atorvastatin 10 mg daily for 6 weeks vs atorvastatin 20 mg daily for 6 weeks vs	above drug treatment thresholds established by NCEP ATP III, with established CHD or CHD risk equivalent with an LDL-C ≥130 mg/dL, no established CHD or CHD risk equivalent, with ≥2 risk factors conferring a 10-year risk for CHD ≥10% and ≤20% with an LDL-C ≥130 mg/dL, no established CHD or CHD risk equivalent, with ≥2 risk factors conferring a 10-year risk for CHD <10% with an LDL-C ≥160 mg/dL; and no established CHD or CHD risk equivalent, with ≥2 risk factors, and with LDL-C ≥190 mg/dL, TG ≤350 mg/dL, ALT, AST, or CK level ≤1.5 times the ULN, serum creatinine ≤1.5 mg/dL, and hemoglobin A_{1C} <9.0% in patients with diabetes		baseline in LDL-C at each mg-equivalent statin dose comparison, percent change from baseline in HDL-C, percentage of subjects that reached NCEP ATP III LDL-C goal	Simvastatin-ezetimibe 10/20 mg combination therapy was associated with a significant reduction in LDL-C from baseline at 6 weeks, compared with atorvastatin 10 mg (50.6% vs 36.1%; *P*<0.001), and atorvastatin 20 mg therapy (50.6% vs 43.7%; *P*<0.001). Simvastatin-ezetimibe 10/40 mg combination therapy was associated with a significant reduction in LDL-C from baseline at 6 weeks, compared with atorvastatin 40 mg (57.4% vs 48.3%; *P*<0.001). Simvastatin-ezetimibe 10/80 mg combination therapy was associated with a significant reduction in LDL-C from baseline at 6 weeks, compared with atorvastatin 80 mg (58.6% vs 52.9%; *P*<0.001). Averaged across all doses, simvastatin-ezetimibe combination therapy was associated with a significant increase in HDL-C from baseline at 6 weeks, compared with atorvastatin (7.9% vs 4.3%; *P*<0.001). A greater proportion of patients reached their NCEP ATP III LDL-C goal at 6 weeks with simvastatin-ezetimibe combination therapy (averaged across all doses), compared with atorvastatin therapy (89.7% vs 81.1%; *P*<0.001). A greater proportion of patients with a CHD or a CHD risk equivalent reached their NCEP ATP III LDL-C goals of <100 mg/dL at 6 weeks with simvastatin-ezetimibe combination therapy (averaged across all doses), compared with atorvastatin therapy (85.4% vs 70%; *P*<0.001). A greater proportion of patients with a CHD or a CHD risk equivalent reached their NCEP ATP III LDL-C goals of <70 mg/dL at 6 weeks with simvastatin-ezetimibe combination therapy

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
atorvastatin 40 mg daily for 6 weeks vs atorvastatin 80 mg daily for 6 weeks				(averaged across all doses), compared with atorvastatin therapy (45.3% vs 20.5%; *P*<0.001). Averaged across all doses, simvastatin-ezetimibe combination therapy was associated with a significant increase in the risk of ALT/AST elevation >3 times the ULN, compared with atorvastatin therapy (*P*=0.006).
Constance et al[49] Atorvastatin 20 mg daily for 6 weeks, following a 4-week atorvastatin 10 mg run-in period vs ezetimibe 10 mg daily added to simvastatin 20 mg daily, separate entities, for 6 weeks, following a 4-week atorvastatin 10 mg run-in period vs ezetimibe 10 mg daily added to simvastatin 40 mg daily, separate entities, for 6 weeks, following a 4-week atorvastatin 10 mg run-in period	DB, MC, PG, RCT Patients ≥18 years of age, with type 2 diabetes, hemoglobin A_{1C} ≤10%, ALT/AST levels <1.5 times the ULN, CK <1.5 times the ULN; patients were excluded if they had congestive heart failure NYHA classes III- IV, MI, CABG or angioplasty within 3 months, uncontrolled HTN or endocrine/metabolic disease, renal dysfunction or nephrotic syndrome, alcohol consumption >14 drinks per week and treatment with excluded concomitant medications	N=661 6 weeks	Primary: Change from baseline in LDL-C at 6 weeks Secondary: Change from baseline in total cholesterol, HDL-C, TG, non–HDL-C, apo B, LDL-C:HDL-C ratio, and TC:HDL-C ratio	Primary: Across all doses, patients on the simvastatin-ezetimibe combination therapy experienced a statistically significant LDL-C reduction from baseline compared with the atorvastatin 20 mg monotherapy group (*P*≤0.001). Secondary: Across all doses, patients on the simvastatin-ezetimibe combination therapy experienced a statistically significant reduction from baseline in total cholesterol, non-HDL, apo B, LDL:HDL cholesterol ratio, and TC:HDL ratio compared with the atorvastatin 20 mg monotherapy group (*P*≤0.001). Patients on the simvastatin-ezetimibe 10/40 mg combination therapy experienced a statistically significant reduction in CRP from baseline compared with the atorvastatin 20 mg monotherapy group (*P*=0.006). Significantly greater proportion of patients randomized to the simvastatin-ezetimibe 10/20 mg and 10/40 mg combination therapy achieved LDL-C <2.5 mmol/L, compared to the atorvastatin 20 mg group (90.5%, 87%, and 70.4%, respectively; *P*≤0.001). The incidence of drug-related adverse effects was similar in the simvastatin-ezetimibe 10/20 mg and 10/40 mg combination therapy and atorvastatin monotherapy groups (0.5%, 0.5%, and 2.3%, respectively; *P* value not reported).
Pearson, et al[50]	MA	N=4,373	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Ezetimibe 10 mg daily for 12 weeks vs ezetimibe 10 mg daily added to simvastatin 10 mg, 20 mg, 40 mg, or 80 mg daily for 12 weeks, separate entities vs simvastatin 10 mg, 20 mg, 40 mg, or 80 mg daily for 12 weeks vs atorvastatin 10 mg, 20 mg, 40 mg, or 80 mg daily for 12 weeks vs placebo	Three identical, prospective 12-week studies randomizing patients to placebo, ezetimibe, ezetimibe with simvastatin or simvastatin alone, and one phase III double-blind, active-controlled study allocating patients to simvastatin-ezetimibe or atorvastatin for 6 weeks	(4 studies) Up to 12 weeks	Change from baseline in LDL-C level, CRP, proportion of patients reaching LDL-C target (<100 mg/dL, or <70 mg/dL) Secondary: Not reported	Across all doses, patients on the simvastatin-ezetimibe combination therapy experienced a statistically significant LDL-C reduction from baseline compared with the simvastatin monotherapy group (52.5% vs 38%; *P*<0.001). Across all doses, patients on the simvastatin-ezetimibe combination therapy experienced a statistically significant LDL-C reduction from baseline compared with the atorvastatin monotherapy group (53.4% vs 45.3%; *P*<0.001). Across all doses, patients on the simvastatin-ezetimibe combination therapy experienced a statistically significant CRP reduction from baseline compared with the simvastatin monotherapy group (31% vs 14.3%; *P*<0.001). Patients on the simvastatin-ezetimibe combination therapy experienced a similar CRP reduction from baseline compared with the atorvastatin monotherapy group (25.1% vs 24.8%; *P* value not reported). Significantly greater proportion of patients randomized to the simvastatin-ezetimibe combination therapy achieved LDL-C <100 mg/dL, compared to the simvastatin group (78.9% vs 43.1%; *P*<0.001). Significantly greater proportion of patients randomized to the simvastatin-ezetimibe combination therapy achieved LDL-C <70 mg/dL, compared to the simvastatin group (37% vs 5.7%; *P*<0.001). Significantly greater proportion of patients randomized to the simvastatin-ezetimibe combination therapy achieved LDL-C <100 mg/dL, compared to the atorvastatin group (79.8% vs 61.9%; *P*<0.001). Significantly greater proportion of patients randomized to the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				simvastatin-ezetimibe combination therapy achieved LDL-C <70 mg/dL, compared to the atorvastatin group (36.2% vs 16.8%; *P*<0.001). Secondary: Not reported
Piorkowski et al[51] Atorvastatin 10 mg daily in addition to ezetimibe 10 mg daily, separate entities vs atorvastatin 40 mg	RCT Patients between 18 and 80 years of age with clinically stable angiographically documented CHD and LDL-C >2.5 mmol/L despite ongoing atorvastatin 10-20 mg daily, receiving aspirin and clopidogrel; patients were excluded if they had a history of an MI or CK elevation within the last 4 weeks, recent warfarin treatment, tumors, severe renal insufficiency, active liver disease, liver cirrhosis, unexplained transaminase elevation, recent antibiotic therapy, or known alcohol abuse	N=56 4 weeks	Primary: Reduction in LDL-C, TG, change in liver transaminases, CK, HDL from baseline, percentage of patients achieving the ATP III LDL-C goal (≤2.5 mmol/L) Secondary: Not reported	Primary: There were no statistically significant differences from baseline in liver transaminases, CK, or HDL in either group (*P* value not reported). Both groups exhibited a statistically significant reduction in LDL-C from baseline (*P*<0.005). There was no statistically significant difference between the two groups in the percentage of patients achieving the ATP III LDL-C goal (≤2.5 mmol/L) (*P* value not reported). There was no statistically significant difference between the two groups in degree of LDL-C reduction from baseline (*P* value not reported). Both the atorvastatin 40 mg and the combination therapy groups exhibited a statistically significant reduction in triglyceride level from baseline (*P*<0.005 and *P*<0.05, respectively). Secondary: Not reported
Ballantyne, Weiss et al[52] EXPLORER	MC, OL, PG, RCT Patients ≥18 years of	N=469 6 weeks	Primary: Percentage of patients achieving the ATP III	Primary: Significantly greater proportion of patients randomized to the combination therapy achieved their LDL-C goal compared to the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Ezetimibe 10 mg, in addition to rosuvastatin 40 mg daily, separate entities, for 6 weeks vs rosuvastatin 40 mg daily for 6 weeks	age with primary hypercholesterolemia and CHD or clinical evidence of atherosclerosis or a CHD risk equivalent (10-year CHD risk score >20%), and mean LDL-C between 160 mg/dL and 250 mg/dL with the two last measurements within 15% of each other, and TG <400 mg/dL; patients were excluded if they were women on hormonal therapy, taking statins within 6 weeks, potent CYP3A4 inhibitors within 5 weeks, oral corticosteroids started within 6 weeks or verapamil within 4 days of study onset; patients were also excluded if they had ALT/AST or CK >1.5 times the ULN, poorly controlled, newly diagnosed diabetes type 1 or 2, or had changed their antidiabetic therapy within 3 months of		LDL-C goal (<100 mg/dL) at 6 weeks Secondary: Change from baseline in LDL-C, total cholesterol, TG, HDL, non-HDL cholesterol, LDL:HDL cholesterol, TC:HDL, non-HDL:HDL, apo B, apo AI, CRP	monotherapy group (94% vs 79.1%; *P*<0.001). Secondary: Patients on the combination therapy experienced a significantly greater reduction from baseline in LDL-C compared to the monotherapy group (70% vs 57%; *P*<0.001). Patients on the combination therapy experienced a significantly greater reduction from baseline in total cholesterol compared to the monotherapy group (51% vs 42%; *P*<0.001). Patients on the combination therapy experienced a significantly greater reduction from baseline in non-HDL cholesterol compared to the monotherapy group (65% vs 52%; *P*<0.001). Patients on the combination therapy experienced a significantly greater reduction from baseline in TG compared to the monotherapy group (35% vs 25%; *P*<0.001). Patients on the combination therapy experienced a significantly greater reduction from baseline in LDL:HDL cholesterol compared to the monotherapy group (72% vs 60%; *P*<0.001). Patients on the combination therapy experienced a significantly greater reduction from baseline in TC:HDL cholesterol compared to the monotherapy group (56% vs 45%; *P*<0.001). Patients on the combination therapy experienced a significantly greater reduction from baseline in non-HDL/HDL cholesterol compared to the monotherapy group (67% vs 55%; *P*<0.001). Patients on the combination therapy experienced a significantly greater reduction from baseline in apo B compared to the monotherapy group (56% vs 45%; *P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	baseline, had uncontrolled HTN, or body mass index ≥30 kg/m^2			Patients on the combination therapy experienced a significantly greater reduction from baseline in CRP compared to the monotherapy group (46% vs 29%; *P*<0.001). There was no statistically significant difference in HDL cholesterol increase (*P*=0.151) or apo AI reduction (*P*=0.202) between the combination therapy and rosuvastatin monotherapy groups. The frequency and types of adverse events were similar across the combination and monotherapy groups (31.5% and 33.5%, respectively; *P* value not reported).
Farnier et al[53] Simvastatin-ezetimibe 10 mg/20 mg for 12 weeks, combination product vs simvastatin-ezetimibe 10 mg/20 mg, combination product, in addition to fenofibrate 160 mg for 12 weeks vs fenofibrate 160 mg for 12 weeks vs placebo for 12 weeks	DB, I, MC, PG, RCT Patients ≥18 years of age with mixed hypercholesterolemia, no CHD or a CHD risk equivalent disease (except for diabetes), or 10-year CHD risk score >20% according to the NCEP ATP III criteria	N=611 12 weeks	Primary: Percent change from baseline in LDL-C Secondary: Percent change from baseline in total cholesterol, TG, HDL, non-HDL cholesterol, LDL:HDL cholesterol, TC:HDL, non-HDL/HDL, apo B	Primary: Simvastatin-ezetimibe/fenofibrate group exhibited significant reduction in LDL-C from baseline compared with the fenofibrate monotherapy group (45.8% vs 15.7%; *P*<0.05). There was no significant difference between LDL-C reduction seen with the simvastatin-ezetimibe/fenofibrate therapy and simvastatin-ezetimibe therapy (45.8% vs 47.1%; *P*>0.2). Secondary: Simvastatin-ezetimibe/fenofibrate group exhibited significant reduction from baseline in non-HDL cholesterol, TG, and apo B compared with the other treatment groups (*P*<0.01). There was no significant difference between total cholesterol reduction seen with the simvastatin-ezetimibe/fenofibrate therapy and simvastatin-ezetimibe therapy (38.7% vs 35.4%; *P*>0.05). Simvastatin-ezetimibe/fenofibrate group exhibited significant increase from baseline in HDL cholesterol compared with the simvastatin-ezetimibe group (18.7% vs 9.3%; *P*<0.01). Simvastatin-ezetimibe/fenofibrate group exhibited significant reduction from baseline in LDL:HDL cholesterol, TC:HDL

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				compared with the simvastatin-ezetimibe group (*P*=0.03). There was no significant difference between the percentage of patients able to reach their LDL-C goal with the simvastatin-ezetimibe/fenofibrate therapy and simvastatin-ezetimibe therapy (88.5% vs 92.9%; *P* value not reported).
Kastelein et al[54] ENHANCE Simvastatin 80 mg daily and placebo vs simvastatin 80 mg daily and ezetimibe 10 mg daily	DB, MC, PRO, RCT Men and women between the ages of 30 and 75 years with FH regardless of their previous treatment with lipid-lowering drugs, baseline LDL-C at least 210 mg/dL without treatment; patients were excluded if they had high-grade stenosis or occlusion of the carotid artery, history of carotid endarterectomy or carotid stenting, homozygous FH, NYHA class III or IV congestive heart failure, cardiac arrhythmia, angina pectoris or recent cardiovascular events	N=720 24 months (plus 6-week run-in period with placebo)	Primary Change in mean carotid artery IMT (defined as average of means of far wall IMT of right and left common carotid arteries and bulbs and internal carotid arteries) Secondary: Proportion of patients with regression in the mean carotid artery IMT or new carotid artery plaques of more than 1.3 mm, change from baseline in mean maximal carotid artery IMT and average mean IMT of carotid and common femoral arteries, lipid parameters, CRP, adverse events	Primary The mean change in the carotid artery IMT was 0.0058±0.0037 mm in the simvastatin monotherapy group and 0.0111±0.0038 mm in the simvastatin-ezetimibe group (*P*=0.29). Secondary: There was no significant difference in the proportion of patients with regression in the mean carotid artery IMT (44.4% vs 45.3%; *P*=0.92) or new plaque formation (2.8% vs 4.7%; *P*=0.20) receiving simvastatin vs simvastatin-ezetimibe, respectively. No significant change from baseline was reported in the mean maximum carotid artery IMT (0.0103±0.0049 mm and 0.0175±0.0049 mm, respectively; *P*=0.27). No significant changes were observed between study groups regarding mean measures of IMT of the common carotid artery (*P*=0.93), carotid bulb (*P*=0.37), internal carotid artery (*P*=0.21) and femoral artery (*P*=0.16) or average of the mean values for carotid and femoral artery IMT (*P*=0.15). After 24 months, mean LDL-C decreased by 39.1 mg/dL in the simvastatin group and by 55.6 mg/dL in the combination group (between-group difference of 16.5%; *P*<0.01). Reductions in TG (between-group difference of 6.6%; *P*<0.01) and CRP (between-group difference of 25.7%; *P*<0.01) were significantly higher with simvastatin-ezetimibe than simvastatin alone.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Adverse events (29.5% vs 34.2%; *P*=0.18) and discontinuation rates (9.4% vs 8.1%; *P*=0.56) were similar between simvastatin monotherapy and the combination therapy.
Homozygous Familial Hypercholesterolemia (HoFH)				
Gagné et al[55] Statin 40 mg for up to 14 weeks, followed by the addition of ezetimibe 10 mg daily for another 12 weeks, separate entities vs statin 40 mg for up to 14 weeks, followed by titration to 80 mg daily and addition of ezetimibe 10 mg daily for another 12 weeks, separate entities vs statin 40 mg for up to 14 weeks, followed by titration to 80 mg daily Statins used in the study included simvastatin and atorvastatin.	DB, MC, RCT Patients ≥12 years old (or with body weight ≥40 kg) with HoFH, LDL-C ≥100 mg/dL and TG ≤350 mg/dL (if on atorvastatin or simvastatin 40 mg/day); patients were excluded if they had liver disease, ALT or AST >2 times the ULN, significant renal disease, unstable coronary syndromes or advanced congestive heart failure, or ongoing treatment with fibric acid derivatives	N=50 26 weeks	Primary: Percent change in LDL-C from baseline to the end of treatment period Secondary: Percent change from baseline in total cholesterol, TG, HDL-C, the ratios of LDL-C:HDL-C and TC:HDL-C, non–HDL-C, apo B, apo AI, and CRP	Primary: LDL-C was reduced more by the addition of ezetimibe 10 mg to the statin than by doubling the dose of statin (20.7% vs 6.7%; *P*=0.007). Secondary: Total cholesterol was reduced more by the addition of ezetimibe 10 mg to the statin than by doubling the dose of statin (18.7% vs 5.3%; *P*<0.01). There was no statistically significant difference in any of the other secondary outcome measures between the two groups (*P*>0.05).

Study abbreviations: CI=confidence interval, CS=comparative study, DB=double blind, DD=double dummy, ER=extended release, ES=extension study, FU=follow-up, HR=hazard ratio, I=international, MA=meta-analysis, MC=multicenter, OR=odds ratio, OL=open label, PC=placebo-controlled, PG=parallel group, PRO=prospective trial, RCT=randomized controlled trial, RR=risk ratio, SB=single blind, SA=subanalysis

Miscellaneous abbreviations: ALT=alanine transaminase, ACS=acute coronary syndrome, AMI=acute myocardial infarction, AST=aspartate transaminase, DBP=diastolic blood pressure, CABG=coronary artery bypass graft, CAD=coronary artery disease, CHD=coronary heart disease, CK=creatine kinase, CRP=C-reactive protein, CVD=cerebrovascular disease, FBG=fasting blood

glucose, HDL-C=high density lipoprotein cholesterol, HTN=hypertension, LDL-C=low density lipoprotein cholesterol, MI=myocardial infarction, NCEP ATP =National Cholesterol Education Program Adult Treatment Panel, NYHA=New York Heart Association, PCI=percutaneous intervention, TC=total cholesterol, TG=triglycerides, upper limit of normal

IX. Conclusions

The combination HMG-CoA reductase inhibitors (statins) are FDA-approved for the treatment of primary hypercholesterolemia.[7,10,11] Atorvastatin-amlodipine and lovastatin-niacin combination products are also indicated for the prevention of cardiovascular events.[9,10] Simvastatin-ezetimibe is not FDA-approved for either primary or secondary prevention of cardiovascular events.[6] All products are formulated for once-daily oral administration. None of the products in this class are available generically. In general, the pharmacokinetic, pharmacologic, drug-interaction, and side-effect parameters with the combination statins are similar to their separate constituents.

The combination statins have demonstrated a significant benefit in reducing total cholesterol, low-density lipoprotein cholesterol (LDL-C), triglycerides, and increasing high-density lipoprotein cholesterol (HDL-C).[1,2,4] Statins are used as first-line agents for the treatment of hypercholesterolemia and prevention of cardiovascular events.[1] Niacin may increase HDL-C and lower triglycerides to a greater degree compared to statin monotherapy.[2,11,30,31] When used in combination with statin therapy, patients evaluated in clinical studies were able to achieve greater LDL-C reduction compared to either niacin or statin monotherapy. Ezetimibe may be used as adjunctive therapy to statins in helping patients reach their NCEP ATP III targets for lipid levels.[4,5]

Although studies have shown that the combination of ezetimibe and a statin is more efficacious in improving lipid parameters than monotherapy with either agent, the recently published results of the ENHANCE trial (Effect of Combination Ezetimibe and High-Dose Simvastatin vs Simvastatin Alone on the Atherosclerotic Process in Patients with Heterozygous Familial Hypercholesterolemia) did not show that these reductions led to better clinical outomes.[54] The ENHANCE trial consisted of 720 patients with familial hypercholesterolemia with a primary end point of mean change in the intima-media thickness measured at three sites in the carotid artery. No significant difference was found in this primary end point between the treatment groups (simvastatin-ezetimibe 80/10 mg compared to patients treated with simvastatin 80 mg alone) during the two-year study period. Combination therapy with ezetimibe and simvastatin significantly lowered LDL-C by 16.5% compared to simvastatin alone. Additional studies are necessary to determine if the combination of ezetimibe plus a statin results in better clinical outcomes since no trial has yet demonstrated a reduction of cardiovascular outcomes with either ezetimibe alone or in combination therapy with a statin.[56,57]

The NCEP ATP III guidelines designate statins as first-line agents for the treatment of patients with hypercholesterolemia, failing therapeutic lifestyle modification, at high risk for cardiovascular events as well as patients suffering from heterozygous familial hypercholesterolemia.[13,14] Therapy should be adjusted to the recommended LDL-C goal <100 mg/dL in high-risk patients; however, an LDL-C goal of <70 mg/dL can be a therapeutic option for patients with coronary heart disease or those at very high risk. If LDL-C goal is not reached after 6 weeks of statin therapy, either an elevation of dose or the addition of a second agent, such as ezetimibe or niacin, is (according to current guidelines)appropriate. Furthermore, niacin may be preferred among patients with high triglycerides or low HDL-C levels. The European Guidelines on Cardiovascular Disease Prevention suggest that ezetimibe can be used in patients with active liver disease.[18] Otherwise, ezetimibe's primary beneficial effect is add-on therapy to statins. The guidelines do not directly address the role of statin fixed-dose combination products.

X. Recommendations

In recognition that studies have confirmed that the efficacy and safety of the combination products are similar to the individual agents when administered separately and that the lipid-lowering aspects of the drugs in this class are comparable, no changes are recommended to the current approval criteria.

Advicor® and Simcor® are preferred on The Office of Vermont Health Access (OVHA) preferred drug list.

Caduet ® requires prior authorization with the following approval criteria:

- The prescriber must provide a clinically valid reason for the use of the requested medication.

Vytorin® requires prior authorization with the following approval criteria:

- The patient has had an inadequate response to both generic simvastatin and Crestor®.

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